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National Toxicology Program

Fiscal Year 1987 Annual Plan

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service

COMPLETED

ORIGINAL

NOTES TO THE READER

Availability

The National Toxicology Program (NTP) Annual Plan for Fiscal Year 1987 may be obtained by writing or calling:

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National Toxicology Program
P. O. Box 12233
Research Triangle Park, NC 27709
(919-541-3991; FTS 629-3991)

Errors or Omissions

Although every effort is made to ensure that the Annual Plan is error free, mistakes may occur. Any errors or omissions noted by the reader in the body of the Annual Plan, the appendices or the indexes, should be called to the attention of:

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Questions of Additional Information

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If readers of the Annual Plan are aware of planned or ongoing studies on chemicals mentioned in the Plan, they are encouraged to make such information known to the NTP, so that unnecessary duplicative studies can be avoided or minimized.

NATIONAL TOXICOLOGY PROGRAM
FISCAL YEAR 1987
ANNUAL PLAN

DEPARTMENT OF HEALTH AND HUMAN SERVICES
U.S. PUBLIC HEALTH SERVICE

II

NATIONAL TOXICOLOGY PROGRAM

ANNUAL PLAN

FOR

FISCAL YEAR 1987

National Cancer Institute/National Institutes of Health
National Institute of Environmental Health Sciences/National Institutes of Health
National Center for Toxicological Research/Food and Drug Administration
National Institute for Occupational Safety and Health/Centers for Disease Control

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May 1987

National Toxicology Program

Public Health Service

Department of Health and Human Services

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL TOXICOLOGY PROGRAM

Annual Plan for Fiscal Year 1987

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EXECUTIVE SUMMARY
NATIONAL TOXICOLOGY PROGRAM
ANNUAL PLAN FOR FISCAL YEAR 1987

The Secretary of Health and Human Services established the National Toxicology Program to coordinate and strengthen the Department's activities in characterizing the toxicity of chemicals. The Program is mandated by the Secretary with:

(1) broadening the spectrum of toxicologic information obtained on selected chemicals;

(2) increasing the numbers of chemicals studied, within funding limits;

(3) developing and validating tests and protocols responsive to regulatory needs; and

(4) communicating Program plans and results to government agencies, the medical and scientific communities, and the public.

Prior to the Program's establishment in 1978, a variety of Public Health Service agencies tested toxic substances -- some in programs dating back to the 1940s. However, with the increased public concern about toxic substances in the 1970s, it became apparent that this testing capacity, which had been used for specific agency interests or mandates, should be coordinated to serve common public health concerns. This was the goal with which the Program was established.

The National Toxicology Program (NTP) coordinates toxicology and related programs of the National Institutes of Health's NIEHS (NIH/NIEHS), the FDA's National Center for Toxicological Research (FDA/NCTR), and the Centers for Disease Control's National Institute for Occupational Safety and Health (CDC/NIOSH). The NCI was originally a major funding agency; however, its primary participating component, the Carcinogenesis Bioassay Program, was transferred to the NIEHS by the Secretary in 1981. The NCI remains active on the NTP Executive Committee (see below).

The NTP is administered by Dr. David Rall, who is also the Director of the NIEHS which represents the majority of NTP resources. Program directions are overseen by an Executive Committee made up of the heads of Federal health research and regulatory agencies. Program scientific quality is overseen and peer reviewed by an independent Board of Scientific Counselors. Scientific quality is augmented internally through intensive review of chemical selection and design of toxicology studies on selected chemicals, along with various measures of quality assurance of the NTP studies. Nominations of chemicals for toxicology studies are made by all participating agencies and are also encouraged from all sectors of the public.

Like many scientific fields, toxicology is a resource-intensive endeavor, expensive in terms of both time and money. As it enters its ninth year, however, the Program demonstrates increasing maturity, and a new interweaving of toxicology testing with applied and basic research.

First, the NTP has successfully established an integrated program for studying chemicals which simultaneously addresses multiple toxicological endpoints using assay protocols specifically tailored to each chemical. Thus, the NTP has expanded the traditional two-year carcinogenesis bioassay into a comprehensive toxicology study which can provide definitive information not only on a chemical's potential to cause cancer in experimental animals, but also on genetic toxicity, chemical disposition, major organ toxicity, and effects on fertility and reproduction. Other endpoints examined in specific cases include neurobehavioral or immunologic toxicity, and endocrine effects.

At the same time, the NTP is devoting increasing efforts to the development, validation, and application of test methodologies that are more rapid, less expensive, or of increased sensitivity and specificity for various toxicological endpoints. For instance, recent research being conducted by the NIEHS is building on the increased knowledge of oncogenes in the carcinogenesis process.

Finally, the very body of NTP test data -- an expanding body of comprehensive, comparable, reliable test results -- is itself emerging as a research tool for developing or evaluating assay methods, e.g., recent evaluations of short-term genetic toxicology tests for their specificity and sensitivity as predictors of carcinogenicity, or for helping refine our understanding of mechanisms of toxicology. Toxicological characterization can be an immediate, effective tool in prevention of chemically induced disease; in the long run, this growing body of data can become its driving force.

Scientific Accomplishments in FY 1986 and Plans for FY 1987

As noted above, the common thread that characterizes the NTP is the toxicological characterization of chemicals and substances to which humans are or may be exposed. This ranges from trying to identify chemicals which may have toxic potential by performing toxicological studies, through conducting studies to improve or develop better assays to characterize toxicity, to the peer review and communication of the results. An ancillary objective is development of information on the mechanism(s) of toxicity of chemicals.

Toxicology research and applied studies activities are divided into four, occasionally overlapping, major program areas: cellular and genetic toxicology; carcinogenesis; reproductive and developmental toxicology; and toxicological characterization. The last area covers activities in cardiac, cutaneous, immunologic, neurobehavioral, pulmonary and renal toxicologies as well as studies oriented to specific chemicals or chemical classes, and chemical disposition and chemical pathology.

The NTP's activities in toxicology research, testing, and methods development are summarized under the four major program areas below:

Cellular and Genetic Toxicology -- The focus of programs in this area is to develop, evaluate, validate and use short term *in vitro* and *in vivo* assays for detecting potential genotoxic and carcinogenic effects of chemicals; to use these and established assays to detect and characterize chemicals that may pose a genetic or carcinogenic effect to humans; to reduce the need for and/or assist in setting priorities for long-term animal studies; and to conduct research aimed at understanding the mechanisms of chemically induced cellular and genetic toxicity.

The genetic toxicity of chemicals nominated and selected by the Program is evaluated initially through use of four in vitro assay systems. In FY 1986, assays were completed for mutagenic effects on 182 chemicals in microbial cells (Salmonella), on 33 chemicals in fruit flies (Drosophila), and on 75 chemicals in mammalian cells (L5178Y mouse lymphoma). Studies were completed on 63 chemicals for cytogenetic effects in mammalian cells (Chinese hamster ovary, CHO). In FY 1987, testing will continue at similar levels in these in vitro assay systems.

Development and validation of in vitro and in vivo assay methods are important components of efforts to improve detection and prediction of carcinogenic and mutagenic activities of chemicals. Assay systems which either measure genetic effects that are important in humans or use human cells to evaluate genetic toxicity of chemicals are especially valuable. Among in vitro assays is one in yeast to measure chromosomal gains or losses (known as aneuploidy) which contribute markedly to genetic disease burden in humans, and one to measure genetic toxicity in human cells (fibroblasts). Whole animal (in vivo) studies are looking at cytogenetic effects of chemicals in rodent bone marrow and human white blood cells (lymphocytes). Efforts continue to measure and compare across three complementary assay systems the induction by chemicals of germ cell (heritable) mutations in mice.

Principal efforts of the NIEHS program during FY 1986 and FY 1987 were to complete adequate genetic toxicity evaluation of 73 chemicals for which good data are available on carcinogenicity or non carcinogenicity in NTP long-term rodent studies. This exercise will provide a highly objective data base for evaluating predictiveness of assay systems for genetic toxicity and carcinogenicity of chemicals. The data base will aid in design of prechronic whole animal studies, in determining whether long-term studies need to be done, and in providing insights for studies to characterize carcinogenic mechanisms for non-mutagenic carcinogens.

Carcinogenesis Research and Applied Studies -- The two-year carcinogenicity study in rodents (usually rats or mice), especially tailored for each chemical, remains the most definitive method for identifying chemical carcinogens. Prechronic (14-day and 90-day) studies serve to provide data on toxicity and chemical disposition and to aid in setting doses for two-year studies. Two-year (chronic) studies now commonly use three or more doses, include interim sacrifice groups to assess chronic toxicity uncomplicated by aging changes, and occasionally include "stop" experiments where exposure to chemicals is terminated prior to two years so that determination can be made as to whether or not neoplastic lesions progress or regress.

During FY 1986, at the NIEHS the draft technical reports of the findings for 19 two-year studies were approved in public session by the peer review panel associated with the NTP Board of Scientific Counselors. Categories (levels of evidence) of interpretive conclusions used to describe the strength of evidence for carcinogenicity for each study result were modified and a list of qualifying key factors added after considerable public input and extensive discussion by the Board. In FY 1987, the NTP expects to complete 27 two-year studies through peer review, while beginning 33 prechronic and 12 chronic studies. The focus for ongoing studies at NCTR are structurally similar antihistamines while at NIOSH emphasis is given to assessing carcinogenic potential of complex mixtures encountered by workers, modification of carcinogenic potential by known and suspected promoters and carcinogens in the workplace, and evaluation of occupational factors that may influence carcinogenicity.

Research and development activities ongoing or to begin at NIEHS in FY 1987 include: (1) evaluating moderate dietary restriction on incidence of spontaneous tumors in rodents; (2) investigating nature and incidence of specific neoplastic lesions in rodents in response to several orally administered vegetable oils; (3) studies comparing activation of oncogenes in spontaneous tumors compared with chemically-induced tumors in rodents; and (4) evaluating the usefulness of microencapsulation for oral administration of volatile, reactive, or unpalatable chemicals. Some of these initiatives are responsive to recommendations by the NTP Board of Scientific Counselors and the report of its Ad Hoc Panel on Chemical Carcinogenesis Testing and Evaluation.

Reproductive and Developmental Toxicology -- Activities in this program area focus on developing a range of techniques for evaluating potential toxic effects of chemical exposure on the reproductive system and developing embryo as well as improving and validating current assays for uncovering such effects. Two well established assay systems are used to routinely evaluate suspect chemicals. The sperm morphology and vaginal cytology evaluation (SMVCE) has become a standard part of 90-day prechronic toxicity studies, and, in FY 1986, over 20 chemicals were evaluated for SMVCE. Conventional teratology testing continues to be used with 13 studies on seven chemicals completed during FY 1986 while a similar number of completions are expected in FY 1987. A consensus workshop in May 1986 affirmed the usefulness of the short term *in vivo* reproductive toxicity assay for accurately detecting reproductive toxicants. The fourth year of studies was completed on the fertility assessment by continuous breeding assay which as currently designed evaluates effects on fertility and offspring for two generations exposed to a chemical. Results from this system and the short-term *in vivo* assay are used in setting priorities for conventional teratology testing.

A number of assay systems were or are in various stages of development and validation. Progress was made on techniques to examine chemical toxicity to the ovaries. Two *in vitro* teratogenesis screening systems continue to be studied. During FY 1986, 44 coded chemicals (including both known teratogens and non-teratogens) were tested in the *in vitro* systems. Work continues using cultured Sertoli cells to define the site of action of chemicals believed to act on the testes. Efforts continue to improve on ability to characterize toxicity of chemicals to newborn relative to adult animals, and to explore the role of chemicals in the milk in the induction of toxicity to nursing newborn.

Toxicological Characterization -- Emphasis remains on more completely characterizing the toxicologic profile of a chemical, especially in prechronic studies. In addition to obtaining chemical disposition and genetic toxicology data, and measuring effects on fertility and reproduction, information may be obtained on other potential target organs such as the nervous, immune, renal and hematopoietic systems. Efforts in pathology have led to improvement in quality of the pathology data and to assurances that both tumor and non-tumor diagnoses in prechronic and two-year studies are consistent and complete.

Research and development activities are highlighted as follows:

Chemical Disposition: Most chemicals chosen for long-term toxicology and carcinogenesis studies undergo some degree of evaluation as to how they are absorbed, distributed, metabolized and excreted by the body (chemical disposition), usually during the prechronic phases, and often includes comparisons of chemical disposition after exposure of animals by more than one route of administration. Special studies included: (1) comparative assessment of dermal vs. oral absorption of some highly halogenated compounds; (2) in-depth disposition studies after inhalation exposure of animals to 1,3-butadiene and its structural analog isoprene, and benzene, which along with development of methods for measuring their metabolism in human tissues could provide data useful for risk assessment; (3) further studies on age-related changes in chemical metabolism and disposition. Analytical methods are also being developed and applied to measuring chemicals and metabolites in human body fluids.

Renal Toxicology: Efforts were focused on development of culture techniques for isolated kidney tubules and intact renal cells for measuring toxicity *in vitro*.

Immunotoxicology: A comprehensive screening panel was used to assess several chemicals of special interest to the NTP for their potential to induce immune alterations or hypersensitivity. Studies are being conducted to develop a model system in the mouse which will allow the assessment of adverse effects of chemicals on neutrophils. Neutrophils constitute the main cellular defense system of higher organisms against bacteria. Research efforts have centered on: (1) examining immunotoxic effects of chlorinated dibenzodioxins, especially TCDD; (2) studying chemicals which alter arachidonic acid metabolism (arachidonic acid is a precursor molecule of prostaglandins, biologically active chemicals); and (3) elucidating the effects of antifolate chemicals on immune (B cell) functions. Antifolates, such as methotrexate, are used as cancer chemotherapeutic agents.

Neurobehavioral Toxicology: A World Health Organization behavioral test battery will be used in FY 1987 to assess worker populations. A study continues on measuring behavioral performance in human volunteers exposed to spray paint solvents. Research is primarily concerned with examining the effects and mechanisms of chemical toxicity to the central nervous system, especially of certain organochlorine compounds such as DDT and chlordecone (Kepone).

Pulmonary Toxicology: Short-term inhalation toxicology studies are being conducted on chemicals of current or continuing public health significance including methyl isocyanate, 1,3-butadiene, methylene chloride, and chemicals used in the semiconductor industry, especially arsine gas and gallium arsenide. The asthma causing potential of vanadium pentoxide after inhalation exposure was confirmed and characterized using pulmonary function and immunologic assays. Studies are also progressing to develop a monkey model for delayed asthma induced by exposure to occupational chemicals.

Studies on Chemical Classes or Complex Mixtures: Among class studies for various toxic endpoints are those on: (1) metals - the salts of antimony, cobalt, chromium, iron, mercury and nickel; (2) 1,3-butadiene and analogs chloroprene and isoprene; and (3) the aminobenzothiazoles. Studies on close structural analogs often provide data on how slight differences in molecules may affect toxic properties of chemicals. As part of the Superfund project, mixtures of chemicals ranging from two to 28 per mixture will be investigated for toxicity during FY 1986 and FY 1987.

Administrative Highlights and Activities

Chemical Nomination and Selection -- This process is integral to the effective long-term operation of the NTP with respect to both toxicological studies of chemicals using current methodologies and the development and validation of new methodologies. During FY 1986, 42 chemicals were nominated to the NTP for extensive toxicological study. The Executive Committee selected eight chemicals as FY 1986 priority chemicals for in-depth toxicologic evaluation. Two of them, t-butylhydroquinone and styrene, were designated as priority chemicals by NTP participating agencies, which results in quicker evaluation.

Resources and Planning Assumptions -- The NTP relies on voluntary allocations from its three member DHHS agencies, the amounts of which are specified in memoranda of understanding after yearly appropriations are known. Using current allocations, the budget for FY 1987 would provide for a funding level of $77.9 million compared with FY 1986 actual obligations of $77.0 million. As in past years, most NTP resources will be spent on studying chemicals for carcinogenic, mutagenic, teratogenic, and other target organ toxic effects. As expected, two-year toxicology and carcinogenesis studies account for a large portion of these resources. Continuing emphasis will be given to development, validation and application of in vitro and in vivo short-term tests which will serve both to better characterize toxicity of selected chemicals and to help set priorities for long-term studies.

Oversight and Review -- As noted, Program policy oversight is provided by the Executive Committee. Composed of the heads of health research and regulatory agencies, the Committee meets three to four times yearly, and serves as NTP's major advisory group on research and testing needs, on selection and priority setting for specific chemicals to be studied, and as a forum for discussion of science policy issues and information exchange among agency heads.

The NTP Board of Scientific Counselors, composed of eight non-governmental scientists, reviews the Program for scientific adequacy. The Board held two meetings in FY 1986. At the first, the Board peer reviewed the five program areas of the NIEHS/NTP Chemical Pathology Branch, and reviewed and made recommendations on seven chemicals nominated for study by the NTP. At the second meeting, the Board peer reviewed the three major areas (reproduction, developmental toxicology, and short-term tests) of the NTP Reproductive and Developmental Toxicology programs. The Board also discussed and made recommendations for suggested modifications in the levels of evidence of carcinogenicity used by the NTP in evaluative conclusions in its Technical Reports.

NTP program activities are discussed in more detail in the following chapters. For scientific program areas and support (coordinative management) activities, information on FY 1986 efforts is separated from planned activities for FY 1987, and current programs and projects are associated with a contact person. Addresses and phone numbers for contact persons are listed in Appendix A.

INTRODUCTION

The National Toxicology Program (NTP) begins its ninth year in FY 1987, having been established within the Public Health Service of the Department of Health and Human Services in November 1978. The broad goals of the NTP are to coordinate and strengthen the Department's activities in the testing of chemicals of public health concern, to increase efforts to develop and validate new and better integrated test methods, and to provide needed information to regulatory and research agencies.

Historical Background

The earliest Federally mandated attempts to address chemical toxicity took place in the pharmaceutical and food additive industries, where extensive safety testing was required by the Federal Food, Drug, and Cosmetic Act. Although this testing was often directed primarily at acute effects, the Food and Drug Administration (FDA), starting in the 1940s carried out many long-term feeding studies with food chemicals and pesticides. Occupational safety and health components of Health and Human Services (HHS) also conducted long-term studies during the period 1940-1970 directed particularly at liver and lung diseases and occupational cancer. In the 1960s the National Cancer Institute (NCI) began a series of projects which heavily relied on rodents to evaluate the carcinogenic potential of a wide spectrum of classes of chemical substances. These projects evolved into the NCI Carcinogenesis Bioassay Program, which contributed greatly to knowledge regarding the carcinogenic potential of chemicals.

Paralleling such efforts were research projects that would increase the array of technologies so that capabilities other than life time studies in animals would evolve with the potential to assess the toxicologic properties of chemical substances. NIEHS through its formal mandate became a major coordinating agency in the development and validation of such methodologies.

Throughout this period, major legislative activity was aimed at providing regulatory tools to reduce or prevent exposure to hazardous substances. This new legislation provided not only the means to increase information on toxicity but also increased the regulator's need to know more, so these tools could be used appropriately.

By the latter part of the 1970s, the various Federal agencies were developing or intensifying test programs in a variety of areas in response both to their respective mandates and to pursue general research needs. However, most of these test programs were limited in scope, ignoring exposure sources or toxicities other than the ones of specific interest to the sponsoring agency, and increasing the chances of unnecessary duplication. Thus, it became apparent that the Nation's toxicology testing capacity was not being used to best advantage. Therefore, the Secretary, DHHS, established the National Toxicology Program in 1978. Its goals were: (1) to integrate DHHS activities to permit the most effective use of the Department's resources and to consolidate scientific expertise in areas needing greater development; and (2) to forge stronger links between toxicology research and the needs of the regulatory community. The NTP provides directly or indirectly much of the basic scientific data used by other Federal and State scientific and regulatory agencies as well as private sector organizations that are useful in responding to issues relevant to the effect of chemical substances on human health and the environment.

Objectives of the National Toxicology Program

The NTP helps focus relevant Public Health Service programs on four objectives:

- Broadening the spectrum of toxicologic information which is obtained on selected chemicals;
- Increasing the numbers of chemicals tested, within funding limits;
- Developing and validating tests and protocols responsive to regulatory needs; and
- Communicating plans and results to governmental agencies, the medical and scientific communities, and the public.

Organizational Structure of the NTP

The Program consists of the relevant toxicology activities of the National Institutes of Health's National Institute of Environmental Health Sciences (NIH/NIEHS), the Food and Drug Administration's National Center for Toxicological Research (FDA/NCTR), and the Centers for Disease Control's National Institute for Occupational Safety and Health (CDC/NIOSH). Resources for the Program originate through voluntary allocations from the budgets of these agencies. The NIH's National Cancer Institute (NIH/NCI) was originally a funding agency; however, their primary participating component, the carcinogenesis bioassay program, was transferred by the Secretary to the NIEHS in FY 1981.

Primary program oversight is provided by the NTP Executive Committee. The Committee is made up of the heads of the participating DHHS agencies (including the NCI) as well as the heads of the major non-DHHS regulatory agencies concerned with human health. These agencies are the Occupational Safety and Health Administration (OSHA) of the Department of Labor, the Environmental Protection Agency (EPA), and the Consumer Product Safety Commission (CPSC). Primary scientific oversight is provided by the NTP Board of Scientific Counselors, composed of eight non-Government scientists, and its two standing subcommittees.

The organizational and oversight structure of the NTP is depicted in Figure 1.

Program Operation

The following sections provide brief overviews of the NTP studies process beginning with nomination and proceeding to communication of the findings.

Chemical Nomination and Selection -- The chemical nomination and selection process is critical to the NTP objectives. Member agencies of the NTP along with other diverse sources nominate chemicals for various types of toxicologic testing. Summaries of the data available (called Executive Summaries) are drafted and nominations are evaluated by the Chemical Evaluation Committee (CEC), composed of representatives from the Executive Committee agencies, which recommends the types of studies with a priority rating for each chemical. The nominations with CEC recommendations are posted in the Federal Register for comment, and then are reviewed by the NTP Board of Scientific Counselors. Final decisions for the Program are made by the Executive Committee as whether to test, defer, or delete chemicals nominated for various types of studies. Additionally, under the Superfund Act, chemicals primarily associated with hazardous waste sites are nominated by EPA, the Hazardous Waste Information Evaluation Subcommittee (HWIES) of the DHHS, and/or the CEC. Following review by the HWIES, selected chemicals are studied by the NTP with support provided under an interagency agreement with the Agency for Toxic Substances and Disease Registry.

Toxicology Studies Design -- Following Executive Committee action, each nominated chemical is assigned to a staff scientist (Chemical Manager) at one of the participating agencies; this person has the responsibility to ensure that the chemical receives a complete scientific evaluation. The Chemical Manager prepares an experimental protocol and presents this for approval/modification to the Toxicology Design Review Committee. Following approval and funding allocation, the chemical is studied, usually by a qualified private contract laboratory or by another Government agency or national laboratory through an interagency agreement. In some instances the study is designed to focus on a specific toxicologic endpoint. However, more often the goal is to broaden and deepen the overall toxicological characterization of the chemical including its genetic toxicity, carcinogenicity, reproductive and developmental toxicity, and toxic effects on other target organs such as the immune and nervous systems. Toxicologic characterizations usually include 14-day and 90-day prechronic studies followed in many cases by two-year studies in rats and/or mice.

Quality assurance (QA) is an integral component of prechronic and chronic toxicology and carcinogenesis studies conducted by the NTP whether inhouse or in most cases, in contract laboratories. Good Laboratory Practice (GLP) compliance inspections and in-life data audits of studies are conducted at master agreement contract laboratories. On studies begun before in-life data auditing was initiated, retrospective data audits have been required prior to peer review of the draft study report.

Toxicology Methods Development and Validation -- An equally critical objective of the NTP is to develop and validate better assay methods which may be more sensitive or specific, and hopefully, more rapid (and hence less expensive). Short-term in vitro tests are being developed which show promise for supplementing and, in some cases, supplanting long-term animal studies. To validate assay systems and build data bases, the NTP uses chemicals for which toxicologic data are available from either its own studies or those of others.

Peer Review -- Chemical Managers prepare technical reports presenting and interpreting the findings on a chemical from prechronic, chronic and special studies. After rigorous inhouse review, these reports are peer reviewed by the Technical Reports Review Subcommittee of the NTP Board of Scientific Counselors. Reports on reproductive and developmental toxicity are reviewed by the

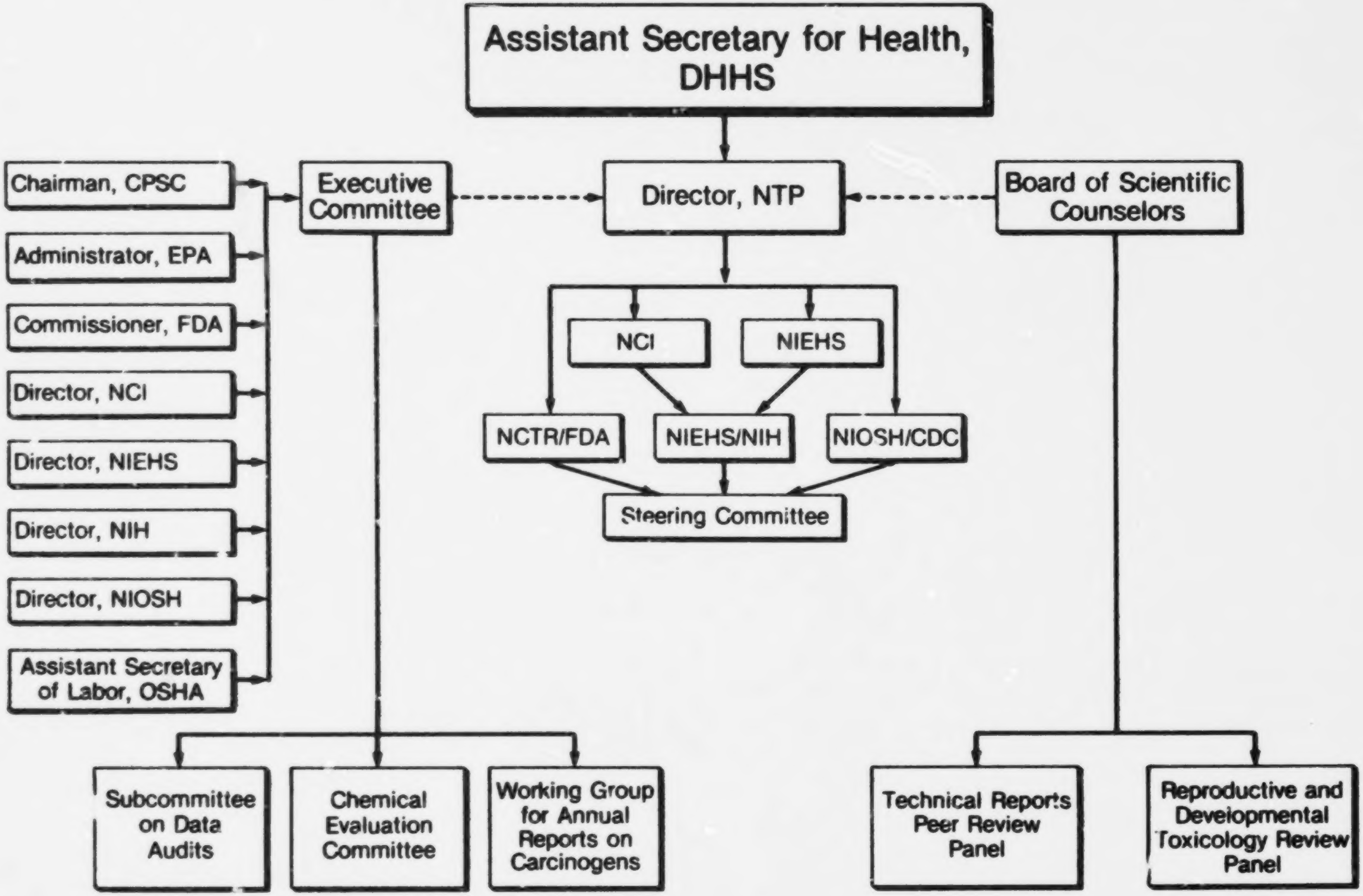
Reproductive and Developmental Toxicology Program Review Subcommittee of the Board. Research and methods development activities for different discipline areas are generally reviewed by the full Board. Most of these reviews are held in sessions open to the public.

Communication of Program Plans and Results -- The communication of reliable scientific information about chemical substances, new or improved assays, and mechanisms of toxic effects, as well as future plans is the final critical objective of the NTP. This is done in many ways. Thousands of readers receive the NTP technical reports, the NTP Annual Plan and its companion volume, the Review of Current DHHS, DOE and EPA Research Related to Toxicology, and the Annual Report on Carcinogens. Lists of chemicals selected for study and of chemicals for which prechronic studies are completed are published in the Federal Register for public information and input. Numerous workshops, conferences and symposia are held to present new findings or discuss problem issues. And, of course, where appropriate, NTP scientists present their findings at meetings and publish them in the open literature.

NTP program activities are discussed in more detail in the following chapters. These cover program resources, oversight and review, coordination and communication, organizational structure, ongoing and planned efforts in toxicology research, testing, and test methods development and validation, chemical nomination and selection, information generation and dissemination, and data management and analysis. Because the chemical nomination and selection process is critical to NTP objectives, we have moved that chapter from its customary position in the back to a more prominent position in the front of the Plan. Information on FY 1986 efforts is separated from planned activities for FY 1987 and beyond, and current programs and projects are associated with a contact person. Accomplishments and plans are also described separately by agency under each scientific and management section.

FIGURE 1

National Toxicology Program (NTP)


Assistant Secretary for Health, DHHS
Chairman, CPSC
Administrator, EPA
Commissioner, FDA
Director, NCI
Director, NIEHS
Director, NIH
Director, NIOSH
Assistant Secretary of Labor, OSHA
Executive Committee
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NCI
NIEHS
NCTR/FDA
NIEHS/NIH
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Steering Committee
Subcommittee on Data Audits
Chemical Evaluation Committee
Working Group for Annual Reports on Carcinogens
Technical Reports Peer Review Panel
Reproductive and Developmental Toxicology Review Panel

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RESOURCES AND PLANNING ASSUMPTIONS

As previously noted, the National Toxicology Program (NTP) consists of toxicology and related activities of the National Institutes of Health's National Institute of Environmental Health Sciences (NIH/NIEHS); the Food and Drug Administration's National Center for Toxicological Research (FDA/NCTR); and the Centers for Disease Control's National Institute for Occupational Safety and Health (CDC/NIOSH). The NIH National Cancer Institute (NIH/NCI), although no longer a funding agency, remains active in the Program through membership on the NTP Executive Committee.

The NTP relies on voluntary allocations from its three member DHHS agencies, the amounts of which are specified in memoranda of understanding after yearly appropriations are known. Obligations in FY 1986 were $77.0 million. Using the member agencies' current allocations, the budget for FY 1987 would provide for a funding level of $77.9 million. The budget for FY 1987 is compared with the actual obligations for the past four fiscal years in Figure 2.

Other Federal agencies also conduct significant toxicology activities. Current information on many of these may be found in the companion volume to the Annual Plan, the FY 1987 Review of Current DHHS, DOE, and EPA Research Related to Toxicology.

As in past years, most NTP resources will be spent on studying chemicals for carcinogenic, mutagenic, teratogenic, and other target organ toxic effects (Figure 3). As may be expected, two-year toxicology and carcinogenesis studies account for a large proportion of these resources.

The NTP will start 33 chemicals in prechronic studies in FY 1987. The information developed in this phase (generally 14- and 90-day studies) provides a better basis for deciding whether chronic studies are warranted. During the prechronic phase, studies of reproductive function, a comprehensive battery of short-term assays measuring cellular and genetic toxicity, measures of chemical disposition, as well as one or more special studies are incorporated into experimental design protocols. Data generated help establish the need for further or more indepth evaluation of a chemical's toxicity. Additionally, all chemicals nominated specifically for genetic toxicologic evaluation are tested in Salmonella and, where indicated, in Drosophila, Chinese hamster ovary cells, and the L5178Y mouse lymphoma mutation system. For those chemicals proceeding to chronic studies, most designs include three dose levels plus controls in both sexes of two rodent species, as well as interim sacrifices to provide more information on chronic toxicity. The NTP will also continue conventional teratology testing at the rate of 10 to 12 studies on 5 to 6 chemicals in FY 1987.

A major problem issue currently confronting the NTP is the need to develop appropriate ways to evaluate the toxicity of complex mixtures of chemicals such as those in hazardous dumps. Primarily as part of Superfund activities, the NTP is developing protocols for both in vivo and in vitro studies to evaluate mixtures of chemicals.

As previously noted, the use of short-term toxicology tests provides data to aid in deciding whether to conduct long-term studies. Over time, more extensive use of existing short-term tests coupled with development, validation and application of improved test systems should reduce the number of chemicals requiring chronic studies. This in turn will allow more emphasis on short-term test development and more information on the chemicals committed to long term studies. (Figure 4 shows the division of funding levels in FY 1986 among toxicology studies, methods development, and test validation for the major program areas of mutagenesis, fertility and reproduction, toxicological characterization and carcinogenesis.) The combination of these composite data will aid health regulatory agencies and the biomedical community in assessment and estimation of human health hazards from chemicals and will help them take steps to prevent or minimize these hazards.

FIGURE 2

AGENCY ORIGIN AND AMOUNTS OF FUNDING (millions)
NATIONAL TOXICOLOGY PROGRAM

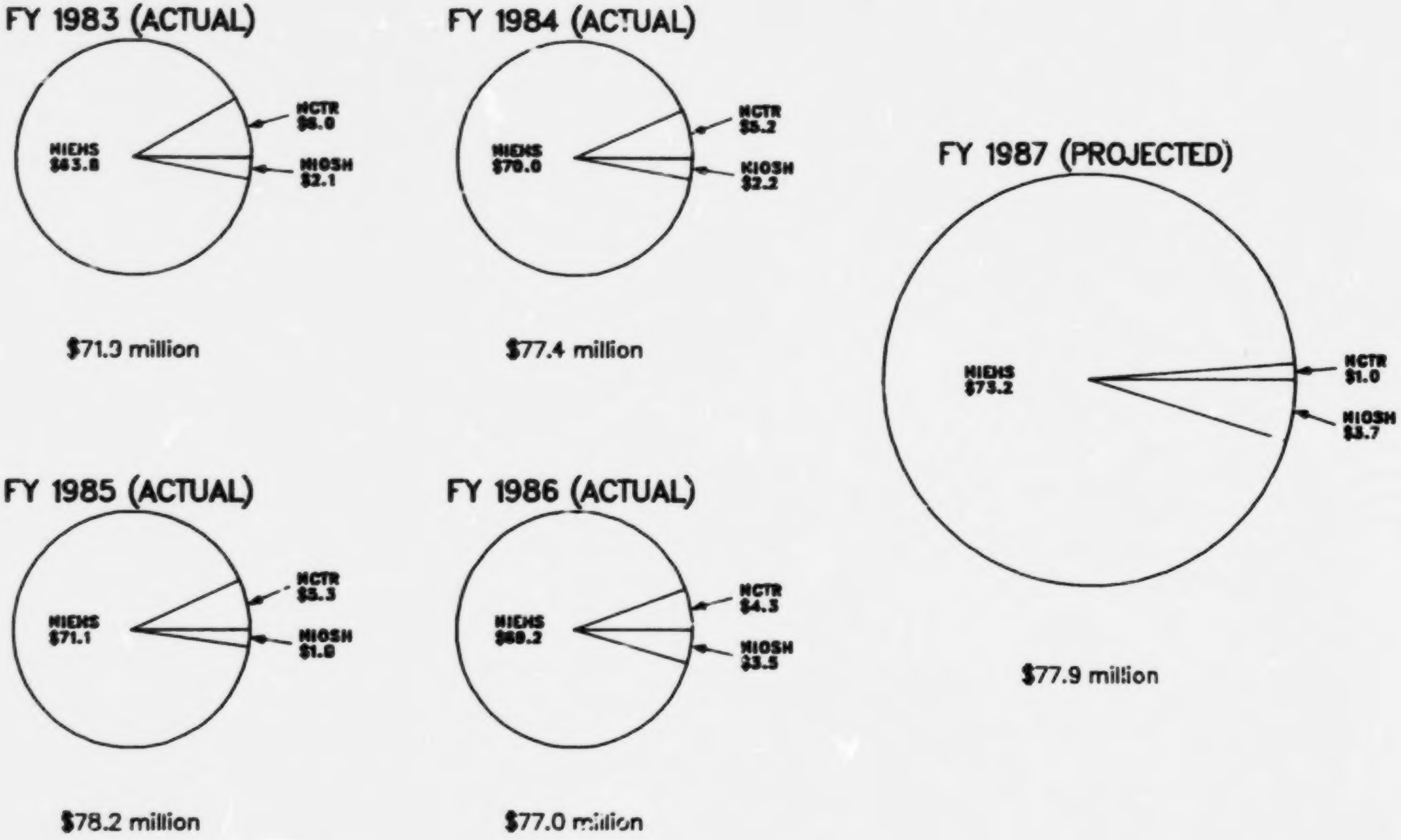

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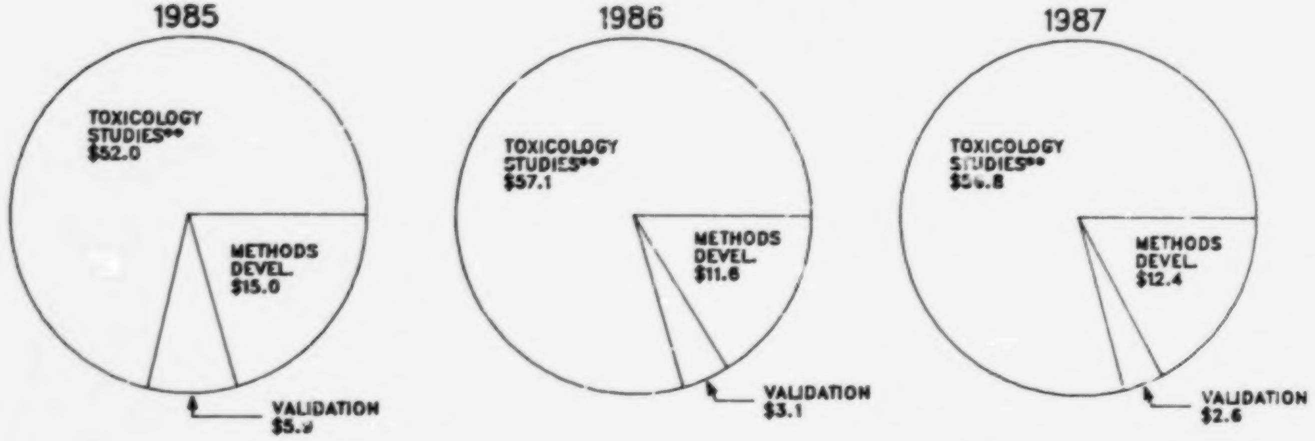
FIGURE 3

FUNDING LEVELS BY PROGRAM ACTIVITIES: FY 1985 -- 1987

NATIONAL TOXICOLOGY PROGRAM (millions)



1985	1986	1987
$72.9	$71.8	$71.8
5.3*	5.2*	6.1*
78.2	77.0	77.9

* Includes other activities such as veterinary pathology training grants, WHO Cooperative Center, indirect operational support, etc.

** Includes prechronic, chronic, immunotoxicology, chemical disposition, teratology, continuous breeding, and mutagenicity studies.

Note: Excludes all Superfund activities

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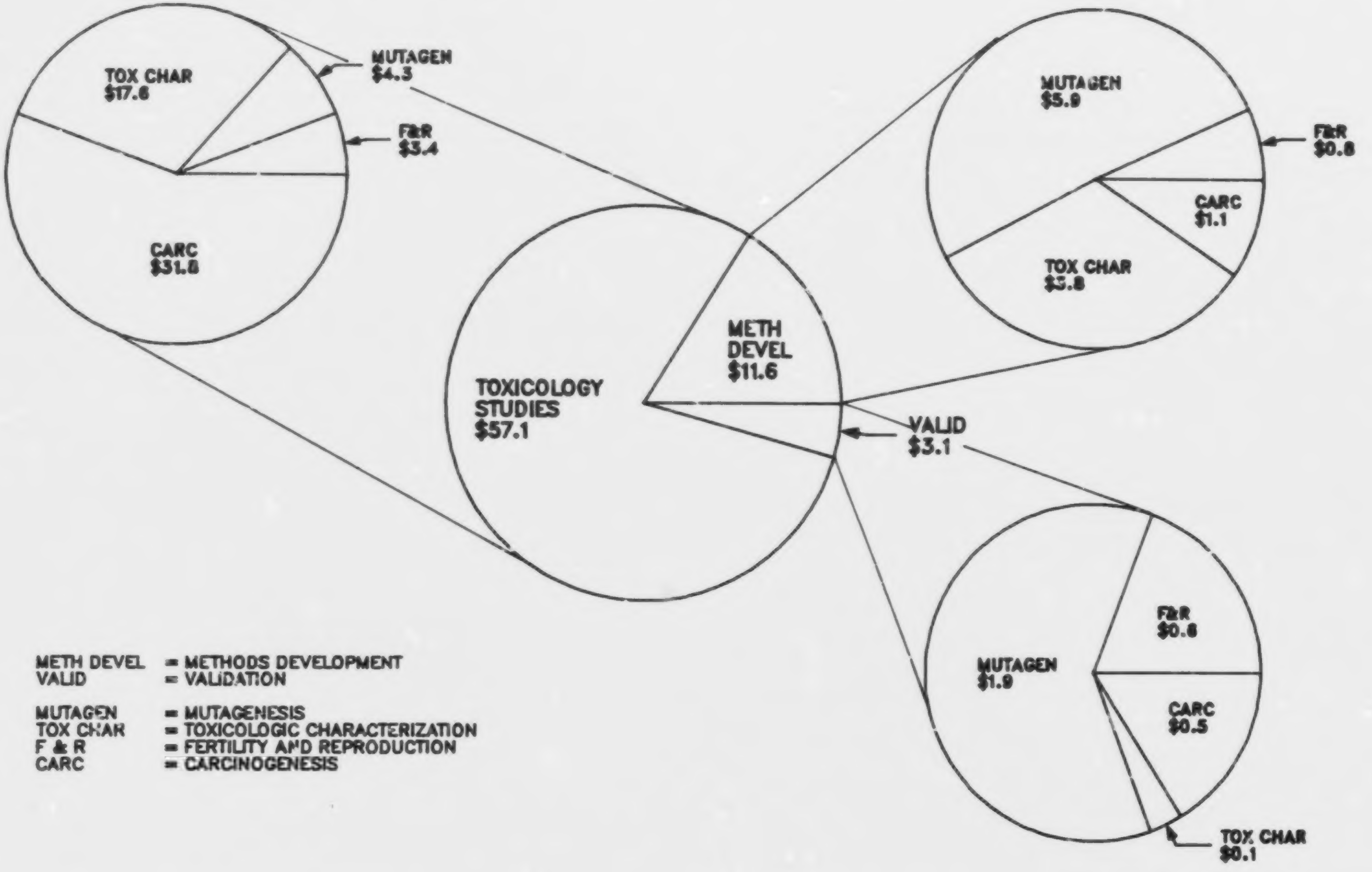
FIGURE 4

FUNDING LEVELS BY PROGRAM ACTIVITIES BY PROGRAM AREA

NATIONAL TOXICOLOGY PROGRAM (millions)
1986



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CHEMICAL NOMINATION AND SELECTION PROCESS

The chemical nomination and selection process remains integral to the effective long-term operation of the NTP with respect to both the testing of chemicals using current methodologies and the validation of new methodologies.

The following discussion briefly summarizes the current NTP chemical nomination and selection process. The process is shown schematically in Figure 5. Accomplishments during FY 1986 and program plans for FY 1987 are described under Coordinative Management Activities in the chapter on Chemical Nomination and Selection Activities. (CONTACT PERSON: Dr. D. Canter)

NTP Chemical Nomination -- Member agencies of the National Toxicology Program and other sources (other Federal agencies, state agencies, the public, labor, industry) submit to the NTP nominations of chemicals for various types of toxicologic testing. The nominating sources are asked to submit the name of the chemical and the particular toxicologic tests desired; the rationale for the nomination; available background data on production, use, exposure, environmental occurrence; and extent of toxicologic characterization in a supporting summary document (see Table 23 in chapter on Chemical Nomination and Selection Activities). However, all nominations are considered regardless of the extent of the information submitted. Nominations should be addressed to: Chemical Nominations, National Toxicology Program, Room 2B-55, Building 31, National Institutes of Health, Bethesda, Maryland 20892.

Nominated chemicals are first reviewed by the NTP chemical selection coordinator to determine which chemicals have been tested, are already on test or scheduled for test, or have been previously considered and rejected for testing by the NTP or its predecessors. This preliminary examination of the nomination involves minimal searches of existing on-line data bases and reference books. The support contractor for the NTP chemical nomination and selection process then examines the available literature, assesses the relevant data and prepares draft Executive Summaries for each chemical. (Draft Executive Summaries are not prepared for chemicals nominated solely for genotoxicity testing.) Included in each draft Executive Summary are: Chemical and Physical Information, Production/Use/Exposure/Environmental/Regulatory Data, Toxicological Effects, and Source of and Reason for Nomination. (CONTACT PERSON: Dr. D. Canter)

Evaluation of Nominated Chemicals -- The draft Executive Summaries are then sent to the Chemical Evaluation Committee (CEC), composed of representatives from the Consumer Product Safety Commission (CPSC), Environmental Protection Agency (EPA), Food and Drug Administration (FDA), Occupational Safety and Health Administration (OSHA), National Cancer Institute (NCI), National Institute of Environmental Health Sciences (NIEHS), National Institute for Occupational Safety and Health (NIOSH), National Center for Toxicological Research (NCTR), and the National Toxicology Program (NTP). The CEC evaluates the draft Executive Summaries and recommends the types of testing to be performed. Primary and secondary reviewers are assigned to each chemical after consideration of the nature of exposure so that, to the extent possible, appropriate regulatory concerns will be addressed. Members are requested to search data bases unique to their agencies for further information on the nominated chemicals (and structurally related compounds) to improve the evaluation process.

At the CEC meeting the primary reviewer for each chemical summarizes the data on that chemical and makes recommendations for testing. The secondary reviewer presents additional information, where available, and also discusses the merits of testing the compound. Following a general discussion, the Committee votes on the recommended types of testing and assigns priorities for the types of testing. The recommendations are based upon whether the chemical satisfies one or more of the eight NTP chemical selection principles (see Table 25 in chapter on Chemical Nomination and Selection Activities). Following the meeting, the contractor revises the Executive Summaries as needed and adds a section on the CEC testing recommendations.

Public Comment -- A Federal Register notice is published which lists the chemicals reviewed by the CEC and the recommended types of testing. Also, the notice solicits comments from interested parties including information on completed, ongoing, and planned testing in the private sector. Responses are requested within 30 days of the date of publication. These steps are taken to enable other individuals and groups to provide data useful to the NTP chemical evaluation process.

Peer Review -- The revised Executive Summaries which include public comments on the nominated chemicals are then forwarded to the NTP Board of Scientific Counselors for review. The Board subsequently meets to evaluate these data and to make testing recommendations based on the available information.

Chemical Selection -- The Board's ratings and comments and pertinent public input are incorporated by staff into final Executive Summaries which are submitted to the NTP Executive Committee. The Committee decides whether to test, defer, or delete each of the nominated chemicals for the various types of study. The Committee also recommends priorities for testing and test methods development/validation to the NTP.

Following Executive Committee action, each chemical is assigned to a chemical manager who assesses the data developed during the NTP chemical evaluation process and other information retrieved from detailed searches of the published literature. The manager also consults with industrial sources on such issues as mode of production, uses, worker exposure, planned or ongoing testing and availability of the chemical for testing. The manager then presents a proposal to the Toxicology Design Review Committee (TDRC) either to perform appropriate toxicologic studies or to delete the chemical from consideration for study. The TDRC, which consists of NTP scientists representing different scientific disciplines, assesses the proposal and either approves the protocols or returns the chemical to the Executive Committee with a recommendation not to pursue testing.

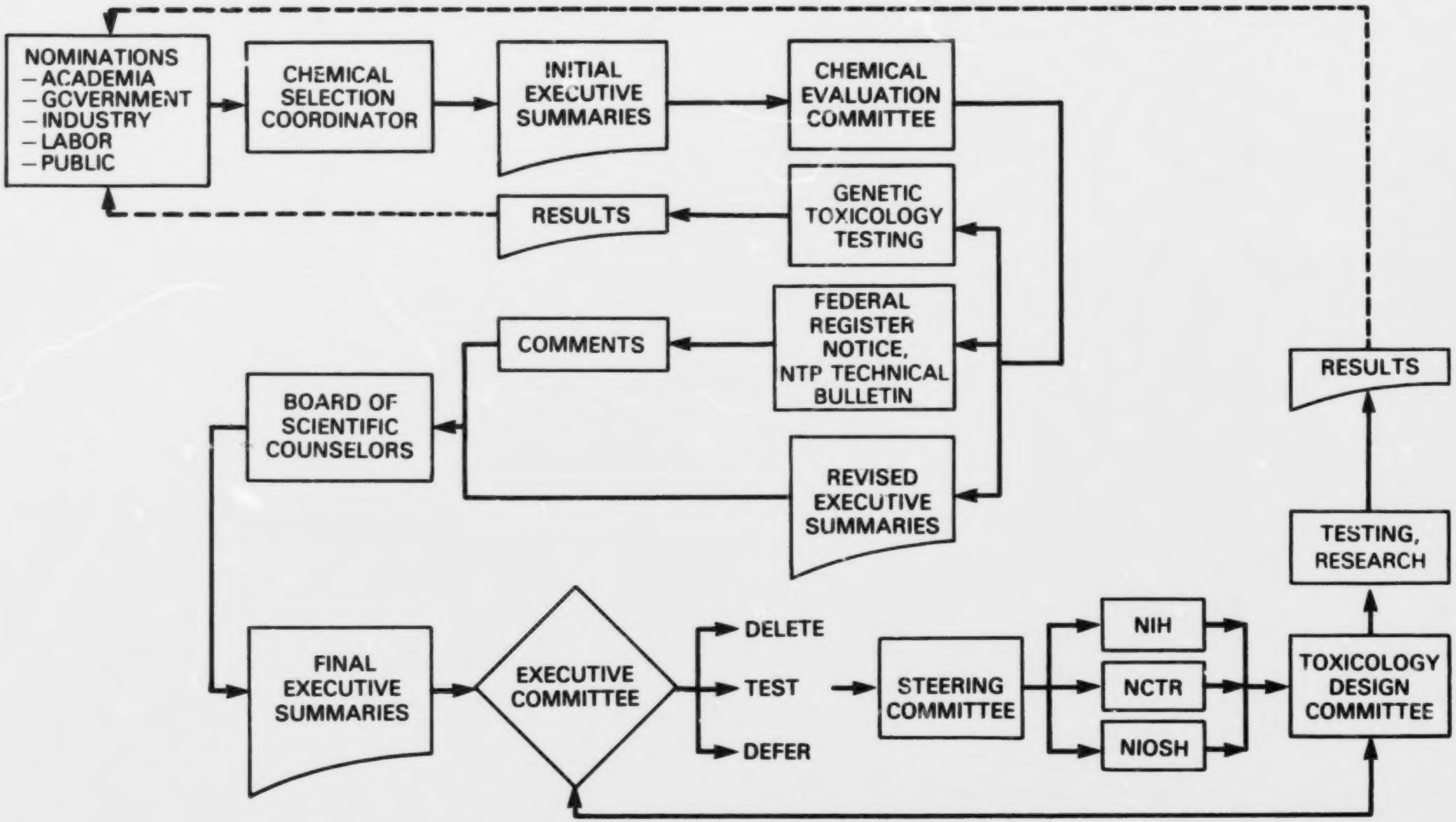
The recommendation may be based upon technical difficulties in testing, budgetary reasons, or the existence of adequate outside testing.

All chemicals selected as a result of this process are then studied as time and resources permit.

Results of toxicological studies of selected chemicals are routinely reviewed to determine whether further types of studies are appropriate. Candidates for additional studies are then resubmitted to the NTP chemical nomination and selection process for evaluation and decision making.

FIGURE 5

NTP CHEMICAL NOMINATION AND SELECTION PROCESS


NOMINATIONS
– ACADEMIA
– GOVERNMENT
– INDUSTRY
– LABOR
– PUBLIC
CHEMICAL SELECTION COORDINATOR
INITIAL EXECUTIVE SUMMARIES
CHEMICAL EVALUATION COMMITTEE
RESULTS
GENETIC TOXICOLOGY TESTING
COMMENTS
FEDERAL REGISTER NOTICE, NTP TECHNICAL BULLETIN
BOARD OF SCIENTIFIC COUNSELORS
REVISED EXECUTIVE SUMMARIES
RESULTS
TESTING, RESEARCH
FINAL EXECUTIVE SUMMARIES
EXECUTIVE COMMITTEE
DELETE
TEST
DEFER
STEERING COMMITTEE
NIH
NCTR
NIOSH
TOXICOLOGY DESIGN COMMITTEE

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OVERSIGHT AND REVIEW

NTP activities are coordinated under the leadership of the Program Director, Dr. David Rall, who for purposes of the NTP reports to the Assistant Secretary for Health, DHHS. However, since the NTP's scientific tasks are so complex and involve integrating several agencies' activities, it is necessary for more than a single body to oversee and review the Program (Figure 1).

GENERAL PROGRAM OVERSIGHT

- EXECUTIVE COMMITTEE

Primary program oversight is provided by the NTP Executive Committee. Composed of the heads of health research and regulatory agencies, it serves as NTP's major advisory group on research and testing needs, on selection and priority-setting for the specific chemicals to be tested, and as a forum for discussion of science policy issues and information exchange among agency heads. The Executive Committee also reviews and approves the NTP Annual Plan. Thus, through the Executive Committee, the NTP assures continuing communication between member health research and health regulatory agencies and receives advice about critical phases of its operation, including program planning and balance.

Members of the Executive Committee as of April 1987 were:

Dr. James B. Wyngaarden, Director, National Institutes of Health (Chairperson)

Dr. Vincent T. DeVita, Jr., Director, National Cancer Institute;

Dr. J. Donald Millar, Director, National Institute for Occupational Safety and Health;

Mr. John A. Pendergrass, Assistant Secretary of Labor for Occupational Safety and Health Administration, Department of Labor;

Dr. David P. Rall, Director, National Institute of Environmental Health Sciences;

Mr. Terrence M. Scanlon, Chairman, Consumer Product Safety Commission;

Mr. Lee Thomas, Administrator, Environmental Protection Agency;

Dr. Robert E. Windom, Assistant Secretary for Health, Department of Health and Human Services (non-voting); and

Dr. Frank E. Young, Commissioner, Food and Drug Administration.

The Chairperson is elected by the Committee and serves a one-year term. The Committee meets three to four times yearly.

SCIENTIFIC OVERSIGHT AND REVIEW

° PEER REVIEW PROCESS

Peer review of NTP projects is a process involving several steps and levels, covering review of project concepts, project proposals, and completed technical reports.

Within the NIEHS, the Toxicology Research and Testing Program Management Committee (see Organization section) performs an initial review of the NIEHS/NTP research and testing proposals. The NTP Board of Scientific Counselors (discussed further below) is the principal body providing scientific oversight and review. The Board performs external peer review of concepts for all NIEHS/NTP and relevant NIOSH contract, cooperative agreement, and inter-agency agreement proposals to advise on their relevance, need, and priority.

All research protocols and contract proposals for NIOSH projects requiring one or more person years undergo formal peer review, utilizing at least two extramural consultants. These peer reviews are announced in the Federal Register and are open to the public. Continuation reviews utilizing extramural consultation are also held for projects entering the fourth year. In addition, the NIOSH Board of Scientific Counselors advises on the scientific merit of NIOSH research.

Scientific oversight and review of personnel and other programs are provided to the NCTR by its Science Advisory Board.

Once grant applications or contract proposals for projects are submitted to the NIEHS/NTP, they are evaluated for scientific merit by the Environmental Health Sciences Review Committee (EHSRC). The EHSRC, which was established as part of the NIH-wide peer review process, is composed of 21 members with expertise in pharmacology, toxicology, pathology, biochemistry, mutagenesis, and clinical disciplines.

When NTP projects are completed and draft technical reports on the results are prepared, the Technical Reports Review Subcommittee of the Board of Scientific Counselors, supplemented by an *ad hoc* panel of expert reviewers, evaluates the reports for technical and scientific merit. The Reproductive and Developmental Toxicology Program Review Subcommittee of the Board provides continuity of peer review for NTP reproductive and developmental toxicology programs.

° NTP BOARD OF SCIENTIFIC COUNSELORS

The Board, composed of eight non-governmental scientists appointed by the Secretary, DHHS, reviews the Program for scientific adequacy and helps identify program needs, assisted on particular issues by scientists with relevant specialties.

Members of the Board at the end of FY 1986 were:

Norman E. Breslow, Ph.D., Professor of Biostatistics, Department of Biostatistics, University of Washington;

Michael A. Gallo, Ph.D., Director of Toxicology, Department of Environmental and Community Medicine, Rutgers University Medical School;

Donald R. Mattison, M.D., Director, Division of Reproductive Pharmacology and Toxicology, and Associate Professor, Department of Obstetrics and Gynecology, University of Arkansas for Health Sciences;

Mortimer L. Mendelsohn, M.D., Ph.D., Associate Director, Biomedical and Environmental Research Program, Lawrence Livermore Laboratory, University of California;

Frederica Perera, Dr. P.H., Assistant Professor, Division of Environmental Sciences, School of Public Health, Columbia University;

Henry C. Pitot, M.D., Ph.D., Professor of Oncology and Pathology, and Director, McArdle Laboratory for Cancer Research, School of Medicine, University of Wisconsin (Chairperson);

Adrianne E. Rogers, M.D., Professor, Department of Pathology, Boston University School of Medicine; and

Robert A. Scala, Ph.D., Senior Scientific Advisor, Research and Environmental Health Division, Exxon Corporation.

The Board meets two or three times a year in public sessions. The two meetings held in FY 1986 are summarized as follows:

October 29-30, 1985, Meeting, Research Triangle Park, North Carolina (NIEHS)

At this meeting, the Board undertook several efforts:

° Aided by several *ad hoc* expert consultants, the Board conducted peer review of the five program areas of the NIEHS/NTP Chemical Pathology Branch: (1) tumor pathology; (2) toxicologic pathology; (3) experimental pathology; (4) clinical pathology; and (5) laboratory animal management.

° The Board considered proposed modifications in the levels of evidence of carcinogenicity categories used to characterize findings for NTP two year studies in rodents, and requested additional revision.

° The Board reviewed seven chemicals (including two glycol ethers and three glycol ether acetates) which had been nominated for testing and previously evaluated by the NTP Chemical Evaluation Committee. The Board's recommendations and priority rankings were incorporated into the final literature summaries sent to the NTP Executive Committee.

° The Board reviewed a NIEHS/NTP concept proposal for studies to be done on contract. The proposal was concerned with evaluating possible strain differences in mice to induction of hepatocarcinogenesis after exposure to known liver carcinogens. The proposal was deferred to allow resolution of Board concerns about cost, chemicals to be studied, cross-strain differences in chemical metabolism, and variables introduced by the animal diet.

March 24-25, 1986, Meeting, Research Triangle Park, North Carolina (NIEHS)

° Aided by several ad hoc expert consultants, the Board conducted peer review of the NTP Reproductive and Development Toxicology programs which cover three major areas of reproduction, developmental toxicology, and short-term tests.

° An intensive discussion drawing on comments from the public and the Board's Technical Reports Review Subcommittee was held to consider suggested modifications in the levels of evidence of carcinogenicity. The discussion concluded with the Board making several specific recommendations to the Program for changes in definitions of the levels and agreeing with inclusion of supporting material for the levels of evidence.

° The Board reviewed 13 chemicals which had been nominated for testing and previously evaluated by the NTP Chemical Evaluation Committee. It recommended testing for three chemicals and deferred action on three other chemicals until results of studies by others could be evaluated. The Board's recommendations and priority rankings for these chemicals were incorporated into the final literature summaries sent to the NTP Executive Committee.

Summary minutes of the two Board meetings held in FY 1986 are available on request. (CONTACT PERSON: Dr. L. G. Hart, NIEHS)

° TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The Technical Reports Review Subcommittee is a standing subcommittee of the Board which provides peer review of the draft reports of long-term NTP toxicology and carcinogenesis studies. It is aided by an ad hoc Panel of Experts chosen primarily to encompass expertise in carcinogenesis, pathology, toxicology and biostatistics.

During FY 1986, the Subcommittee and ad hoc Panel of Experts met in open session in December, March, and August. Peer review was completed on the technical reports for 19 toxicology and carcinogenesis studies. (For listing of studies and results see Tables 9 and 10 in the Carcinogenesis Research and Applied Studies chapter.)

Additionally, the Subcommittee and Panel conducted a special review at the request of the Center for Food Safety and Applied Nutrition, Food and Drug Administration (FDA), meeting on January 8, 1986 in Research Triangle Park to review the data from a chronic carcinogenesis rodent bioassay of the color, FD and C Yellow No. 6.

Summary minutes of these meetings are available on request. (CONTACT PERSON: Dr. L. G. Hart, NIEHS)

The members of the Subcommittee and Panel of Experts during FY 1986 were as follows (beginning and ending of terms):

Subcommittee

- Dr. Jerry B. Hook (Chairperson) (Ended March 1986)
- Dr. Robert A. Scala (Chairperson) (Began March 1986)
- Dr. Michael A. Gallo (Began March 1986)
- Dr. Frederica Perera
- Dr. James Swenberg (Ended March 1986)

Ad Hoc Panel

- Dr. Charles C. Capen, Department of Veterinary Pathobiology, Ohio State University (Began March 1986);
- Dr. Vernon Chinchilli, Department of Biostatistics, Medical College of Virginia (Began March 1986);
- Dr. John J. Crowley, Division of Public Health Science, the Fred Hutchinson Cancer Research Center;
- Dr. Kim Hooper, Department of Health Services, State of California;
- Dr. Donald Hughes, Research Development Department, The Procter and Gamble Company (Began March 1986);
- Dr. Thomas C. Jones, New England Regional Primate Research Center, Harvard Medical School (Ended December 1985);
- Dr. Richard J. Kociba, Dow Chemical USA (Ended December 1985);
- Dr. David Kotelchuck, United Electrical, Radio and Machine Workers of America (Ended December 1985);
- Dr. Franklin E. Mirer, Health and Safety Department, International Union, United Auto Workers;
- Dr. James A. Popp, Department of Experimental Pathology and Toxicology, Chemical Industry Institute of Toxicology (Began March 1986);
- Dr. I. F. H. Purchase, Central Toxicology Laboratory, Imperial Chemical Industries, PLC;
- Dr. Andrew Sivak, Biomedical Science, Arthur D. Little, Inc. (Began March 1986);

- Dr. Steven R. Tannenbaum, Department of Nutrition and Food Science, Massachusetts Institute of Technology (Ended December 1985); and

- Dr. Bruce W. Turnbull, College of Engineering, Cornell University (Ended December 1985).

- REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY PROGRAM REVIEW SUBCOMMITTEE

The Reproductive and Developmental Toxicology Program Review Subcommittee, another standing Subcommittee of the Board, was established to: (1) review concept statements for new contract proposals prior to Board review; (2) advise in the review of general protocols and reports; (3) annually review overall program direction and scope; and (4) assist the Board in its reviews of program progress and quality. Members are selected on the basis of expertise in one or more of the following areas -- structural or behavioral teratology, in vitro teratology, and general or specific aspects of male and female reproductive toxicology.

Although the Subcommittee did not meet formally in FY 1986, most of its members assisted the NTP Board in its review of the NTP Reproductive and Developmental Toxicology program. Minutes which summarize this review are available on request. (CONTACT PERSON: Dr. L. G. Hart, NIEHS)

During FY 1986, the Subcommittee was chaired by Dr. Jeanne Manson. During the last half of the year, Dr. Donald Mattison was chairman. Ad hoc members were as follows:

- Dr. Allan R. Beaudoin, Department of Anatomy, University of Michigan Medical School;

- Dr. Donald E. Hutchings, New York State Psychiatric Institute;

- Dr. Joanne Killinger, Environmental Health Center, Stauffer Chemical Company;

- Dr. Carole A. Kimmel, Reproductive Effects Assessment Group, Environmental Protection Agency;

- Dr. Richard Miller, Department of Obstetrics and Gynecology, University of Rochester Medical Center;

- Dr. Lonnie D. Russell, Department of Physiology, School of Medicine, Southern Illinois University;

- Dr. Richard G. Skalko, Department of Anatomy, College of Medicine, East Tennessee State University; and

- Dr. George Szczech, Burroughs Wellcome Company.

COORDINATION AND COMMUNICATION

Communication of NTP's activities, research findings, testing results and new test methods, as well as coordination of related scientific programs among agencies are keys to NTP's success. Communication is pursued in a number of ways as described below.

COMMUNICATIONS

Reports -- The Annual Plan, which is developed by the DHHS member agencies (NIEHS, NCTR, and NIOSH), is central to the communication and coordination process. The Plan is the principal description of the toxicology research, test development, and chemical testing efforts coordinated among the relevant health research and regulatory agencies; it represents NTP's current strategy for testing, test methods development and validation, and it details the NTP's accomplishments in the preceding fiscal year. Part II of the Annual Plan, the Review of Current DHHS, EPA, and DOE Research Related to Toxicology, describes toxicology activities in other agencies. The Annual Report on Carcinogens provides information on "all substances which are either known to be carcinogens or which may be reasonably anticipated to be carcinogens and to which a significant number of persons residing in the United States are exposed...". Technical reports on all NTP prechronic and chronic toxicology and carcinogenesis studies are developed and made available for public distribution. Finally, program scientists publish their findings in the open literature.

Open Meetings and Exhibits -- These media are important in providing the public an opportunity to comment on and receive information about the Program. For instance, an NTP scientific informational exhibit was presented at the annual meetings of the Teratology Society (July 8-10, 1986) and the Behavioral Teratology Society (July 6-8, 1986). A symposium on selected current program activities was presented at the 1986 Annual Meeting of the Society of Toxicology. The two to three meetings yearly of the NTP Board of Scientific Counselors, its Peer Review Panel, and its Reproductive and Developmental Toxicology Program Review Subcommittee provide frequent opportunities for informing the public and receiving review and comments on NTP programs and specific studies on chemicals.

Additionally, the NTP and NTP participating agencies organize, and sponsor or cosponsor conferences and workshops on topics ranging recently from:

(1) the status of toxicological studies on a specific chemical or class of chemicals of current public health concern, e.g., a conference on March 12 and 13, 1986, at which scientists from the Federal Government, academic and industrial laboratories presented their findings from various kinds of toxicology studies on methyl isocyanate;

(2) assessment of the state-of-the-art and usefulness of toxicologic methodology, e.g., an NIEHS cellular and genetic toxicology collaborative workshop on May 12 to 14, 1986, held to evaluate *in vivo* and *in vitro* short-term model assay systems which have been undergoing development and validation over the last several years for their value in detecting and/or characterizing genetic toxicologic and carcinogenic endpoints; to

(3) evaluations of the status of basic and applied research in a scientific area of interest, e.g., a conference cosponsored by the NTP and two of its agencies, NIEHS and NIOSH, on September 8 to 10, 1986, to discuss biological approaches for mechanistic studies on and assay systems for tumor promoters.

INTERAGENCY COORDINATION

The NTP is structured to enhance information exchange and scientific collaboration among its members and others addressing common problems of chemical toxicology. The common membership on the Executive Committee of the health research and health regulatory agencies is focal. These agencies review and comment on NTP plans, and share information on their activities which are of interest both to the NTP and other member agencies.

The NTP actively seeks to foster exchanges and this interaction is encouraged at all levels of the NTP infrastructure. For instance, the research and regulatory agencies actively nominate chemicals for various types of toxicological studies, and review, evaluate, and rank substances nominated. Key agency staff at OSHA, CPSC, EPA, NCI, NCTR, FDA and NIOSH are invited to the meetings of the Toxicology Design Review Committee, and chemical managers stay in contact with agencies during preparation of study designs on chemicals of interest to them in order to help assure responsiveness to agency concerns. Coordination is encouraged throughout the conduct of the studies and the analysis of results.

Use of NTP Findings by Regulatory Agencies -- The NTP member regulatory agencies then use the NTP test data in considering the need for regulation of these chemicals. Specific examples of agency actions initiated during FY 1986 include:

Environmental Protection Agency (EPA)

The EPA took several actions using NTP results:

- It began a special review of pesticide products containing 1,3-dichloropropene based on the positive finding by NTP in rats and mice (Technical Report [TR] 269), along with other information;
- It promulgated a significant new use rule for pentachloroethane based in part on NTP carcinogenicity findings (TR 232);
- It issued a final testing rule under the Toxic Substances Control Act (TSCA) that requires manufacturers and processors to test 1,2-dichloropropane (DCP) for neurotoxicity, mutagenicity, reproductive and developmental effects and acute and chronic toxicity to marine organisms. Cited were NTP long-term studies (TR 263) and NTP concerns over DCP in drinking water;
- It proposed a significant new use rule under TSCA for 11-aminoundecanoic acid using results of the NTP feed study (TR 216);

Occupational Safety and Health Administration (OSHA)

- In response to referral of 1,3-butadiene by EPA, OSHA concluded that the chemical poses risk to the occupationally exposed population at current OSHA permissible exposure limits, and that risk can be reduced or prevented by promulgation of a revised standard. Results of NTP studies in mice (especially TR 288) were clearly triggers for regulatory analysis and future actions;

- On referral from EPA, OSHA concluded there is an indication that occupational exposure to 4,4'-methylene dianiline (MDA) presents a significant risk to workers that can be prevented or reduced to a significant extent. The most persuasive study was regarded as the NTP study (TR 248); and

Consumer Product Safety Commission (CPSC)

- It proposed rulemaking to establish the status of methylene chloride as a hazardous substance for household products, in part based on NTP inhalation studies (TR 306).

Finally, NTP responds to regulatory agency requests for additional testing of chemicals in order to better elucidate their mechanisms of action or general toxic effects. For example, the agencies requested further studies of 1,3-butadiene. Studies have begun to assess the relationship between exposure level and duration of exposure on the outcome of butadiene induced tumors. Pharmacokinetic studies of butadiene were initiated to determine whether differences in species/strain sensitivities are due to differences in absorption, distribution, metabolism, or excretion. In addition, *in vivo* cytogenetics and teratology studies are in progress.

Collaborative Research and Data Gathering Activities -- Two continuing efforts also illustrate the NTP role in interagency coordination:

Glycol Ethers

The glycol ethers initiative continued in 1986 as a collaborative NTP research effort. While earlier activity focused on reproductive toxicity and teratogenicity of class members, recent emphasis has been given to studying genetic toxicology and long-term toxicologic and carcinogenic potential for members of this class, especially the homologs, ethylene glycol monomethyl-, monoethyl-, and monobutyl ethers.

Phthalates

The NTP/EPA Clearinghouse on Phthalates was created in response to a unanimous recommendation of the Federal health regulatory and research agencies made at the June 1981 Conference on Phthalates. Persons or organizations planning, conducting, or having completed research on the toxicological effects of these compounds are requested to contact Ms. Sharon Soward, NTP/EPA Clearinghouse on Phthalates, Room 1813, Building 18, North Campus, National Institute of Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, North Carolina 27709. Telephone: (919)-541-3418, FTS: 629-3418. The contact person for the EPA is Dr. Laurence Rosenstein. Telephone: (202) 382-3626, FTS: 382-3626.

Research studies on phthalic acid esters by the NIEHS are described in the section on Phthalate Studies in the chapter on Toxicologic Characterization.

Toxicology Data Management System (TDMS) -- The interagency agreement between NIEHS and NCTR was extended for a third year. This will allow continuing implementation of this data management system for collection, storage, and retrieval of carcinogenicity and toxicology data. During FY 1987, transition from NCTR to NIEHS for laboratory liaison, software development and maintenance, and computer operations will be completed. Reports of FY 1986 accomplishments can be found in the Data Management and Analysis chapter.

Superfund Activities -- The NTP conducts toxicology testing on chemicals identified in priority hazardous waste sites or otherwise released into the environment, in support of PHS responsibilities under the Comprehensive Environmental Response, Compensation and Liability Act (Superfund). These chemicals are tested under an interagency agreement with the Agency for Toxic Substances and Disease Registry (ATSDR).

The chemicals that NTP agrees to test are selected from among those identified by EPA as being present in priority hazardous waste sites, and which were nominated for NTP testing by EPA, the Hazardous Waste Information Evaluation Subcommittee (HWIES) of the DHHS (chaired by ATSDR) and/or the NTP Chemical Evaluation Committee. The necessity, nature, and scope of testing are determined by NTP in accordance with the Program's established procedures, and by HWIES. Information on types of studies performed and chemicals being evaluated may be found in the Superfund project section in the chapter on Toxicologic Characterization. (CONTACT PERSONS: Dr. E. Rauckman and Dr. R. Yang, NIEHS)

Other Activities -- NTP staff continue to participate in interagency liaison groups, including the DHHS Committee to Coordinate Environmental Health and Related Programs, the Task Force on Environmental Cancer and Heart and Lung Disease, the Interagency Collaborative Group on Carcinogenesis, and the Chemical Evaluation Committee.

A memorandum of understanding between the NTP and the U.S. Army Medical Research and Development Command (USAMRDC) was renewed until 1986. The agreement serves as authority for specific agreements for conducting joint projects, exchanging compounds for identification and testing, and cross validation of research methodologies.

The NTP interagency agreements with the EPA Laboratory Data Integrity Program and the FDA Office of Regulatory Affairs were renewed for FY 1987. These agreements foster communication and coordinate the exchange of information resulting from quality assurance (QA) inspections conducted at toxicology laboratories of mutual interest under the Good Laboratory Practice

(GLP) Regulations. During FY 1987, the NTP will review a request from the EPA to participate directly in selected GLP inspections performed by the Agency by providing scientists who are knowledgeable in disciplines such as inhalation, genetic, or developmental toxicology or in pathology. (CONTACT PERSONS: Dr. D. Bristol, NIEHS; Dr. D. Goldman, EPA; and Dr. P. Lepore, FDA)

INTERNATIONAL COORDINATION

NTP maintains its varied liaison with a number of international agencies. Scientific exchanges and collaborative research activities are conducted through a variety of mechanisms that extend from informal direct contact between investigators in a number of countries to formal agreements for cooperation between the U. S. and the governments of other countries. NTP is also an active participant in the International Program on Chemical Safety (IPCS), sponsored jointly by the World Health Organization (WHO), the United Nations Environment Program (UNEP) and the International Labor Organization (ILO). Close liaison is also maintained with the WHO's International Agency for Research on Cancer (IARC).

ORGANIZATION

The National Toxicology Program (NTP) is composed of appropriate toxicology and related programs of the National Institutes of Health (NIH), the Centers for Disease Control (CDC), and the Food and Drug Administration (FDA) (Figure 1). The NIH component, the National Institute of Environmental Health Sciences (NIEHS), represents the majority of the NTP support, and is administered by the Director and NTP staff headquartered at NIEHS. The CDC's component, the National Institute for Occupational Safety and Health (NIOSH), and the FDA's component, the National Center for Toxicological Research (NCTR), are not under NTP administrative management.

The NTP Steering Committee, formed in 1980, promotes NTP cooperative working relationships. Composed of the NTP Director; the Director, NCTR; the Director, Division of Biomedical and Behavioral Science, NIOSH; and the Director, Toxicology Research and Testing Program, NIEHS; along with key support staff; the Committee meets three to four times yearly. The Committee reviews ongoing and proposed programs and projects, resolves interagency problems, makes agency allocations for chemicals approved for toxicology study by the Executive Committee, and plans agendas for upcoming NTP meetings. Within each agency are staff who act as coordinators or program leaders in the major NTP scientific and program support segments.

The program segments of the NTP can be grouped broadly into two categories --toxicologic research and chemical characterization activities, and coordinative management activities. These activities are described briefly by agency as follows:

NIEHS -- The Toxicology Research and Testing Program (TRTP) comprises the NIEHS toxicology efforts in basic and applied research and management activities. The TRTP is responsible for all NIEHS/NTP operations and is composed of four branches and a quality assurance group:

- Carcinogenesis and Toxicology Evaluation Branch
    - Designs, conducts, monitors, and interprets toxicologic, carcinogenicity and related studies on chemicals.
    - Develops data that elucidate general and specific mechanisms involved in toxic responses to chemicals.
    - Provides logistical support for coordinating and scheduling the contract laboratory functions. Oversees contract awards and conduct of studies at contract laboratories.
    - Serves as a resource for chemical acquisition and storage, and general laboratory health and safety.
- Cellular and Genetic Toxicology Branch
    - Develops and validates *in vivo* and *in vitro* methods to detect and define effects of chemicals on genetic components.

  - Investigates genetic damage in somatic as well as germ cells.
  - Studies effects of chemicals on experimental organisms and to a far lesser extent on human populations.
- Chemical Pathology Branch
  - Provides pathology support to all segments of the Program, especially critical to long-term toxicology and carcinogenesis studies.
  - Develops standards for neoplastic (tumor) and non-neoplastic (toxic) pathology diagnoses and nomenclature.
  - Develops clinical chemistry parameters for assessing cellular and organ function.
  - Manages laboratory animal breeding and allocation.
- Systemic Toxicology Branch
  - Studies target organ toxicities and develops methods for assessing toxic effects involving immune, pulmonary, reproductive, and renal functions.
  - Performs studies to expand basic knowledge of chemical absorption, distribution, metabolism, and excretion.
- Quality Assurance Group
  - Performs GLP compliance inspections of contract laboratories.
  - Conducts audits of studies in-progress for all work included in NTP Technical Reports.
  - Conducts retrospective data audits on completed two-year carcinogenicity studies and on all NTP Technical Reports.

The four branch chiefs and several other key staff persons form the TRTP Management Committee. The Committee, chaired by the Director, TRTP, meets weekly, and is responsible for planning, review, and implementation of NIEHS/NTP activities.

The Carcinogenesis and Toxicology Evaluation Branch, along with information generation and dissemination activities (managed from the Office of the Director, TRTP), and data management and analysis functions (provided by the Data Management and Analysis group of the NIEHS Biometry and Risk Assessment Program), constitute a major segment of coordinative management activities supporting the toxicology and associated research and testing efforts and provide information on program plans and progress.

NIOSH -- The NTP program of NIOSH consists of research projects and related activities from five divisions: the Division of Biomedical and Behavioral Science; the Division of Respiratory Disease Studies; the Division of Standards Development and Technology Transfer; the Division of Surveillance, Hazard Evaluations and Field Studies; and the Division of Physical Sciences and Engineering. The contributions to the NTP from each of these divisions are outlined below.

- Division of Biomedical and Behavioral Science, Cincinnati, Ohio

  This Division conducts most of NIOSH's research in toxicology. The NTP projects fall into the areas of general toxicology, carcinogenesis, reproductive toxicology, neurotoxicology, and cutaneous toxicology. Inhalation exposures and dermal application are emphasized.

- Division of Respiratory Disease Studies, Morgantown, West Virginia

  This Division conducts research on the mutagenicity of materials found at the workplace. Methods are developed or refined to detect mutagens of occupational significance.

- Division of Standards Development and Technology Transfer, Cincinnati, Ohio

  This Division provides information to NTP in the form of evaluations of published literature on chemical hazards, recommendations for chemicals proposed for evaluation, and other services as requested.

- Division of Surveillance, Hazard Evaluations and Field Studies, Cincinnati, Ohio

  This division provides information on numbers of workers exposed, the occupations and kinds of workplaces involved, and other information found in national occupational exposure surveys. The field studies and health hazard evaluations conducted by this division can also provide information on exposures occurring in the workplace.

- Division of Physical Sciences and Engineering, Cincinnati, Ohio

  This division develops analytical methods relative to NTP compounds, advises on analysis of mixtures that may be tested by NTP, and provides other chemical expertise as needed.

Several scientists from NIOSH serve as chemical managers for chemicals being tested by NTP. Senior scientists from NIOSH are members of the NTP committees concerned with chemical nominations, data auditing, and discipline-specific activities.

NCTR -- The National Center for Toxicological Research (NCTR) supports the NTP in a number of areas. Although the research at the NCTR is conducted in an interdisciplinary manner with each study often being a collaboration by several divisions, the bulk of NCTR's contributions to the NTP is provided by the following divisions:

- Division of Reproductive and Developmental Toxicology

  This division provides project officers and coordinators for NTP reproductive and developmental toxicology studies. The major effort involves an ovarian toxicology screen.

- Division of Genetic Toxicology

  Staff members conduct studies for NTP in the area of cellular and genetic toxicology. This includes the development and validation of *in vitro* and *in vivo* systems for determining genotoxicity of chemicals and the testing of NTP compounds in the primary hepatocyte/DNA repair system.

- Division of Biochemical Toxicology

  Division staff members perform chemical disposition and metabolism studies on NTP chemicals, especially with respect to the activation and inactivation of toxic compounds and the mechanism of action of carcinogens.

- Division of Comparative Toxicology

  This division conducts prechronic and chronic animal studies on NTP chemicals. It conducts research involving toxicity and carcinogenicity of chemicals in whole animal experiments and determines the chemical disposition and metabolism of selected compounds. It also provides staff members who serve as Chemical Managers for chemicals being tested in other contract laboratories.

- Division of Toxicology Data Management Systems

  This division is heavily involved in the development and utilization of computer-based systems for data collection, storage, and evaluation for NTP chronic studies. It coordinates the acquisition and utilization of hardware by various contractors for the long-term studies and the development of software for various NTP programs.

All three member agencies are particularly involved in chemical nomination and selection, and chemical and laboratory test management. Chemical nomination involves the evaluation and priority ranking of chemicals by staff from all the agencies on the Executive Committee. Staff members at each agency are assigned as Chemical Managers for individual compounds to serve as a focus for the scientific aspects of the studies on that chemical. Laboratory management is carried out by scientists serving as project officers, to ensure that each toxicological study is conducted in a proper and timely fashion (see Chemical and Laboratory Management section).

TOXICOLOGY RESEARCH AND APPLIED STUDIES OVERVIEW

From the beginning, a major ongoing objective of the NTP has been to evaluate the potential toxicity of chemicals. Concurrent and evolving over time with this evaluation, emphasis has been placed on broadening and deepening the overall toxicological characterizations of chemicals selected for study. Numerous endpoints for potentially toxic effects, rather than single outcomes such as carcinogenicity or teratogenicity, are examined.

A second major and parallel objective is to develop, improve, and validate more sensitive, rapid, and less expensive methodologies for detecting and characterizing the toxicity of chemicals. Short-term *in vitro* and *in vivo* tests are being developed to supplement and, *in some cases, to supplant long-term* whole animal studies. An ancillary objective is to develop information on the mechanism(s) of toxicity of chemicals.

Toxicology research and applied studies activities are divided into four, occasionally overlapping, major program areas: cellular and genetic toxicology; carcinogenesis; toxicologic characterization; and reproductive and developmental toxicology.

The major research, methods development, and testing activities accomplished in FY 1986 and planned for FY 1987 are summarized below. (More detailed descriptions of specific program activities are given in the following chapters.)

Cellular and Genetic Toxicology -- An overall focus of NTP programs in *this broad area is to develop, evaluate*, validate, and use short-term *in vitro* and *in vivo* assays for detecting potential genotoxic and carcinogenic *effects* of *chemicals*. The assays are used to assess genotoxic risks or events in humans, to aid in the design and interpretation of long-term toxicology and carcinogenesis studies in animals, and to reduce the need for and/or assist in setting priorities for long-term studies. An important underlying effort is directed at understanding the mechanisms of chemically induced cellular and genetic toxicity.

Principal efforts of the NIEHS program during FY 1986 have been to complete adequate genetic toxicity evaluation of 73 chemicals previously tested by the NTP for carcinogenicity in long-term studies in rodents and to conduct an extensive evaluation of both tumorigenic and toxic effects of these chemicals in rodents and their genetic toxicity patterns in various short-term *in vivo* and *in vitro* assays.

The NIEHS continues to evaluate the genetic toxicity of chemicals nominated to the Program through use of four *in vitro* assay systems. In FY 1986, assays were completed for mutagenic *effects on* 182 chemicals in microbial cells (*Salmonella*), on 33 chemicals in *Drosophila*, and on 75 chemicals in mammalian *cells* (*L5178Y* mouse lymphoma). *Testing* was completed on 63 chemicals for cytogenetic effects in mammalian cells (Chinese hamster ovary, CHO). In FY 1987, testing will continue at somewhat higher levels in CHO cells and *Drosophila*, and at lower levels in *Salmonella* and L5178Y mouse lymphoma cells.

Methods development and validation activities include: *in vitro* -- (1) *mammalian cell transformation* - evaluation of three *transformation assays* was completed. These systems, along with the Balb/c 3T3 system, are the most proximate in vitro surrogates of induced neoplasia in vitro. However, more development would be needed to enable use in routine testing; (2) aneuploidy induction in yeast - chromosomal loss or gain contributes significantly to the genetically based disease burden in human populations. A number of coded chemicals have been tested for chromosome loss while in FY 1987 validation with chemicals will begin to determine chromosome gain; (3) human cell assay for genetic toxicity - two approaches are being used. One uses surgically derived human hepatocytes for metabolic activation of chemicals and human fibroblasts as genetic target cells. The other involves attempting to improve the metabolic activating capability of human target cells through hybridization and/or gene transfection techniques so both activation and genetic toxicity can be measured in the same cells.

Methods development and validation activities also include: in vivo -- (1) mouse bone marrow cytogenetics - an in vivo complement to Chinese hamster ovary cells for measuring chromosome aberrations (CAs) and sister chromatid exchanges (SCEs). The 73 selected chemicals are being tested as part of an effort to define the role of the assay in predicting potential carcinogenicity; (2) erythrocyte and bone marrow micronucleus tests - are being studied for their ability to differentiate carcinogenic/non-carcinogenic analogs where both members are genotoxic. The tests are being evaluated using the 73 chemicals as a more economical alternative to mouse bone marrow cytogenetics; (3) human lymphocyte cytogenetics - a standardized protocol has been developed and is being used to measure frequencies of CAs and SCEs in a sample of 480 people. Analyses to date show smokers and females have higher incidences of SCEs than nonsmokers and males. None of the factors studied have shown an effect on CAs.

Under gene transposition assays -- (1) three different methodologies to measure gene transposition in Drosophila have been developed in an effort to determine if chemicals induce transposition; (2) research continues with mouse endogenous retroviral long terminal repeat (LTR) elements for studying gene transposition in environmental carcinogenesis.

Efforts at measuring germinal mutations include the morphological specific locus assay which is, at present, the most practical and reliable means for detecting induced heritable mutations in mammals. The assay is being used with a model mutagen, N-ethyl-N-nitrosourea (ENU), to investigate chemically induced mutation processes in mammalian germ cells, and to test select chemicals, including urethane, platinol and acrylamide, for mouse germ cell mutagenicity. Two other newer assays for heritable effects are being evaluated concurrently, using some of the same chemicals so cross-test comparisons can be made. These are the heritable translocation test and the biochemical specific locus assay.

Intramural research projects include: (1) characterizing the molecular genetics of meiosis and mutagenesis in yeast, and the induction and repair of DNA damage in centromeres; (2) studies defining the role of free radicals in mutagenesis of Salmonella by sodium bisulfite, glutathione and other sulfhydryl-containing chemicals and metals; (3) DNA repair and mutagenesis in Drosophila; (4) development of cell culture systems to study human and rodent differences in carcinogen activation; and (5) in FY 1987, a study of the activation of proviral gene expression by nonmutagenic carcinogens.

At NCTR, 84 chemicals have been completely assessed, with 20 still undergoing analysis, for potential genotoxicity in the primary rat hepatocyte/DNA repair system. This project will be completed in FY 1987.

The NIOSH program is directed at assessing genotoxic risks in the workplace. Efforts included in FY 1986: (1) completed validation with volatile mutagens and carcinogens in the Salmonella arabinose resistant mutagenicity assay. Results indicate the assay is a sensitive system for detection of different types of mutagens; and in FY 1986, continuing in FY 1987; (2) development, modification and validation of the SOS chromotest assay for detecting the genotoxicity of complex mixtures; (3) studies evaluating in vivo/in vitro with in vivo cytogenetic assays using mouse bone marrow and spleen cells for determining potential hazard of chemicals to exposed workers; (4) studies assessing the usefulness of chlorophyllin as an antimutagenic agent; and beginning in FY 1987, (5) development of a system for studying the genotoxicity of industrial chemicals in lung cells using multiple genetic endpoints.

Carcinogenesis Research and Applied Studies -- At NIEHS, the two-year carcinogenicity study continues to be tailored to meet the special testing needs identified for each chemical. The prechronic studies (usually 14-day and 90-day) are employed to develop information about toxicologic effects and disposition of a chemical, to aid in setting doses for chronic studies and, in some cases, to aid in deciding not to proceed with chronic (two-year) studies. Chronic studies now commonly use both sexes of rats and mice, multiple doses, dose-response curves, and pharmacokinetic and chemical disposition considerations. In some cases, groups of animals are killed at 12, 15 or 18 months of exposure so chronic toxicity uncomplicated by aging changes can be assessed, and in other cases, chemical administration is stopped ("stop studies") after exposures ranging from 3 to 21 months and regression/progression of lesions are monitored.

During FY 1986, the ad hoc peer review panel associated with the NTP Board of Scientific Counselors approved draft technical reports on 19 two-year studies. For 12 of these studies, five categories adopted by the NTP in FY 1983 were used to describe the strength of evidence for carcinogenicity for each study result while for the other seven, modified categories (levels) of evidence were used. The levels and qualifying factors were modified after considerable discussion by the Board in March 1986. There were 43 studies in the prechronic phases of toxicology and carcinogenesis studies and 154 studies in the chronic phase at the end of FY 1986. For FY 1987, the NTP has scheduled 33 chemical starts in the prechronic phases and 12 chemical starts in the chronic phase. It is projected that 27 two-year studies will be completed and the draft reports peer reviewed in FY 1987.

Research and methods development activities at NIEHS included: (1) evaluating the effects of moderate dietary restriction in rodents on the incidence of spontaneous tumors and on the sensitivity of two-year studies for detecting chemical carcinogens; (2) continuing development of a rat leukemia model; (3) validating rat liver tumor models for initiation/promotion began in FY 1986 with testing of chemicals; (4) continuing studies comparing activation of oncogenes in chemically induced vs. spontaneous tumors in rodents; and (5) continuing investigation of the nature and etiology of specific lesions in experimental animals, such as proliferative exocrine pancreatic lesions in male rats associated with a vegetable oil gavage vehicle, and forestomach neoplastic lesions in rodents exposed orally to irritant chemicals.

The NCTR program continues to conduct prechronic and chronic toxicology and carcinogenesis evaluations on food additives, animal or human drugs, pesticides, or other chemicals of interest to the FDA and nominated to the NTP. Also continuing is a study examining the relationship between chemical structure and toxicologic endpoints including neoplasia for several structurally similar antihistamines; namely, doxylamine, pyrilamine, and triprolidine. The usefulness of microencapsulation for oral administration of volatile, reactive, or unpalatable chemicals continues to be evaluated at NCTR and NIEHS with comparative bioavailability studies.

At NIOSH, emphasis is given to assessment of the carcinogenic potential of complex mixtures encountered by workers, modification of carcinogenic potential by known and potential promoters and cocarcinogens in the workplace, and evaluation of occupational factors and personal habits that may influence carcinogenicity. Specific ongoing and planned studies include: mesothelioma production by asbestos substitutes; assessment of the cocarcinogenic and tumor promotional potential of asphalt fumes and the major fractions; and further evaluation of the V79 metabolic cooperation system for assaying tumor promotional and cocarcinogenic effects of chemicals. Thirty chemicals will be tested in the V79 system in FY 1987.

Toxicologic Characterization -- At NIEHS, the emphasis remains on more completely characterizing the toxicologic profile of a chemical, especially in prechronic studies. In addition to chemical disposition and genetic toxicology data, and measures of effects on fertility and reproduction, information is obtained on other potential target organs such as the nervous, immune, renal and hematopoietic systems. Efforts in pathology have led to improvement in quality of the pathology data and to assurances that both tumor and non-tumor diagnoses in the two-year studies are consistent and complete.

Efforts in renal toxicology were focused on development of culture techniques for kidney tubules and intact renal cells along with indicators of renal toxicity for testing of chemicals *in vitro*. Studies in cutaneous toxicology divide between evaluating the toxicologic and carcinogenic effects of 19 chemicals using protocols specifically designed for dermal exposure, and development of *in vitro* techniques for measuring dermal absorption and metabolism as well as development of a responsive mouse skin model for initiation/promotion studies.

In the area of immunotoxicology, the comprehensive screening panel was used to assess the immunotoxicity of several chemicals of special interest to the NTP including lithium carbonate, tetra ethyl lead, glutaraldehyde, nitrophenylpentadiene (NPPD) ("Spy Dust"), and methyl isocyanate. Work was initiated on developing a mouse model for assessing adverse effects of chemicals on neutrophils. Research efforts focused on: examining immunotoxic mechanisms of dioxins, especially TCDD; studying chemicals which influence arachidonic acid metabolism; and elucidating the effects of antifolates on B cell functions. In neurobehavioral toxicology, research is primarily concerned with examining the effects and mechanisms of chemical toxicity to the central nervous system, especially of certain organochlorine compounds. In the area of pulmonary toxicology, emphasis is on conducting short-term inhalation studies on chemicals including methyl isocyanate, 1,3-butadiene, methylene chloride, and chemicals used in the semiconductor industry, especially arsine gas and gallium arsenide. Automated chambers have been developed which optimize staff safety in the study of extremely toxic chemicals.

Most chemicals chosen for long-term toxicology and carcinogenesis studies undergo some degree of chemical disposition evaluation, usually during the prechronic phases. Special studies included: (1) comparative assessment of dermal vs. oral absorption of some highly halogenated compounds; (2) in-depth disposition studies after inhalation exposure of animals to 1,3-butadiene and benzene which along with development of methods for measuring chemical metabolism in human tissues can provide data useful for risk assessment; and (3) further studies on age-related changes in chemical metabolism and disposition.

A number of other individual chemicals and chemical classes received attention in FY 1986, and many of these studies will continue in FY 1987. Studies with specific chemicals focused on target organ effects and mechanisms for: (1) the induction of lung lesions by Vitamin E; (2) male infertility due to 1,2-dibromo-3-chloropropane; and (3) hepatotoxicity of methylphenidate and of di-2-ethyl hexyl phthalate (DEHP). Among new or ongoing chemical class studies for various toxic endpoints are those on: (1) the salts of antimony, cobalt, chromium, iron, mercury and nickel; (2) 1,3-butadiene and analogs chloroprene and isoprene; and (3) the aminobenzothiazoles. The benzidine dye initiative will wind down in FY 1987 with completion of chronic studies on several prototypical dyes. As part of the Superfund project, mixtures of chemicals ranging from two to 28 per mixture will be investigated for toxicity during FYs 1986 and 1987.

At NIOSH, toxicologic characterization studies center on pulmonary, cardiac, neurobehavioral and cutaneous toxicology as well as on biological monitoring of chemical metabolites. The asthmagenic potential of vanadium pentoxide after inhalation exposure was investigated using pulmonary function and immunologic assays. Studies are progressing on developing a monkey model for delayed asthma induced by exposure to occupational chemicals. NIOSH will implement use of the World Health Organization (WHO) behavioral test battery in assessing worker populations, and behavioral performance continues to be assessed in humans exposed to ketone spray paint solvents. Cardiac toxicity in rats after exposure to chemicals including allylamines and carbon disulfide is being evaluated with morphologic, biochemical and functional indices. The program in cutaneous toxicology continues to focus on the percutaneous absorption of chemicals, including aniline, benzene, ethyl benzene and toluene, with evaluation of how multiple application affects dermal absorption of volatile compounds. Analytical methods were developed for measuring chemicals and metabolites and used to assay human body fluids for exposure to ketones and glycol ethers. In FY 1987, exposures to 4,4'-methylenebis (orthochloroaniline) (MBOCA), m-DET, carbon disulfide and coal tar pitch will be measured.

At NCTR, detailed metabolism studies of gentian violet in rodents were completed. Mutagenicity in two in vitro systems was assayed for metabolites from both avian and mammalian studies. Tissue and biological fluid levels of sulfamethazine metabolites were measured in rats.

Reproductive and Developmental Toxicology -- This program area continues to focus on developing a range of techniques for evaluating potential toxic effects of chemical exposure on the reproductive system and developing embryo as well as improving and validating current assays for uncovering such effects. In the NCTR program, emphasis is being given to developing techniques for evaluating ovarian toxicity. This effort uses tissues from female animals in NTP continuous breeding studies to investigate the relationship between morphological features of the mouse ovary and chemical-induced effects on fertility.

At NIEHS, evaluation of the fertility assessment by continuous breeding assay was finished with completion of 48 study reports on chemicals from several classes. In FY 1987, the system will be used to test a limited number of chemicals per year and various strains and species will be evaluated to further optimize the system. In FY 1986, 13 conventional teratology studies on seven chemicals were completed while six studies on three chemicals were in progress. The sperm morphology and vaginal cytology evaluations (SMVCE) have become a standard part of 90-day prechronic toxicity studies. In special cases, the SMVCE may be done after nine-month interim sacrifices in chronic studies. Protocols for two in vitro teratogenesis screening systems, the mouse ovarian tumor cell attachment and human embryonic palatal mesenchyme cell assays, have been standardized by two laboratories and testing has been completed on 44 coded compounds in each laboratory. A workshop will evaluate the findings and recommendations for future use will be made. Work will continue using cultured Sertoli cells to define the site of action of specific toxicants. Efforts continue to improve our ability to characterize toxicity of chemicals to neonates relative to adult animals, and to explore the role of lactation in the induction of neonatal toxicity. Studies were completed characterizing the testicular and hepatic toxicity of di-2-ethylhexylphthalate (DEHP) in neonatal and adult rats of different ages. Excretion into the milk and effects on neonates will be determined with DEHP and cimetidine. There are continuing studies on the interactions of different halogenated hydrocarbons and their ability to alter normal development, and studies were conducted in mice to evaluate effects of inhaled methyl isocyanate on reproduction and development.

In the NIOSH program, a workshop was held in May 1986 to evaluate the short-term in vivo reproductive toxicity assay with the consensus being that this was a useful test system for accurately detecting reproductive toxicants. Under a new inhalation reproductive toxicity capability, two chemicals, 1,3-butadiene and n-hexane, were evaluated for induction of dominant lethal mutations in male mice, for effects on sperm head morphology in mice, and for teratogenicity in rats and mice (1,3-butadiene only). Structural and behavioral teratology studies on n-hexane will be done in FY 1987, and studies will begin on other chemicals. Validation of a short-term teratology screening method in Drosophila will continue. Also ongoing are extensive studies on the behavioral teratology of alcohol solvents. Studies continued on the metabolism and excretion of diethylene glycol dimethyl ether and attempts to determine the metabolite(s) responsible. A longitudinal study of human semen characteristics will be completed in FY 1987.

CELLULAR AND GENETIC TOXICOLOGY

The cellular and genetic toxicology programs at the three NTP agencies have some parallel objectives. The NIEHS, through its Cellular and Genetic Toxicology Branch, is involved in development, improvement and validation of short-term tests for mutagens and carcinogens, using short-term tests to detect and characterize chemicals that may pose carcinogenic or genetic risks to humans, and in basic research on mutagenesis and related genetic effects of chemicals.

The NCTR program is focused on developing and validating *in vitro* and *in vivo* systems for determining genotoxicity of chemicals, and on using the primary hepatocyte DNA repair system to detect potential DNA damage induced by chemicals selected by the NTP.

NIOSH is concerned primarily with assessing genotoxic risks at the workplace and developing and using suitable assay systems for monitoring workers for the presence of genotoxic substances or the occurrence of genotoxic events.

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NIEHS CELLULAR AND GENETIC TOXICOLOGY BRANCH

The Cellular and Genetic Toxicology Branch (CGTB) conducts two related programs. The first is directed at understanding the mechanisms of chemically induced cellular and genetic toxicity and the second is related to development, validation and evaluation of test systems for identifying and characterizing the genetic toxicity of chemicals. The field of genetic toxicology evolved from the recognition that radiation and many chemical carcinogens could directly damage cellular DNA and from the belief that *in vitro* or short-term test systems could be developed that would be useful in predicting the potential carcinogenicity for the vast number of chemicals to which humans may be exposed. While carcinogenicity is the primary predictive goal of short-term assays that are being developed or validated by the Branch, another important concern is the potential germ cell mutagenicity or capacity of some chemicals to induce mutations in the germ cells of exposed individuals and thus affect their progeny; this is another potential application of short-term test methods that measure genetic toxicity. Therefore, genetic toxicology in the broad sense identifies substances that, through their induction of gene or chromosomal mutations, give rise to heritable changes in cells and thus lead to the development of neoplasia or filial mutations.

The separate but closely related processes of test system validation and evaluation have been program efforts over the past few years. In our validation efforts the principles of establishing working protocols that can accommodate a variety of different properties and which can be conducted in a way that give a high degree of intra- and inter-laboratory reproducibility have been essential features of our effort. The management of contract projects that fulfill these principles, together with the testing of chemicals under code, has led to the development of a highly objective data base necessary for evaluating test performances. In addition, a major impediment to all previous efforts to evaluate the relative performance of the various *in vitro* short-term test methods has been the absence of an adequate number of compounds that have been tested sufficiently that they can be considered to be noncarcinogens. The National Toxicology Program chronic toxicology and carcinogenesis studies in rodents are one of the few sources of results on a substantial number of chemicals to which animals have been exposed at sufficient concentration for sufficient duration that the chemicals can be classified as non-carcinogens. The principal efforts of the Branch over the past year, therefore, have been to complete adequate genetic toxicity evaluation of 73 chemicals that have been tested under the aegis of the National Toxicology Program in rodents and to conduct an extensive evaluation of both the tumorigenic and toxic effects of these chemicals in rodents and their genetic toxicity patterns in various *in vitro* and *in vivo* short-term genetic toxicity assays.

Program plans for FY 1987 involve completion and presentation of our initial evaluation of the 73 chemicals and defining strategies under which the short-term test information can be used by the National Toxicology Program. We will continue to develop or initiate additional projects directed principally toward the *in vitro* assay of substances that may be classified as non-mutagenic carcinogens. One such effort, for example, will involve the development of methods to measure chemical activation of oncogene expression. There will also be increased emphasis on providing detailed genetic toxicity results both *in vitro* and *in vivo* for chemicals nominated for testing by the National Toxicology Program.

TESTING PROJECTS

- *In Vitro Nonmammalian Test Systems*

Salmonella Mutagenesis Testing -- The *Salmonella* microsome assay with strains TA97, TA98, TA100, TA1535, and TA1537 is being used to test chemicals for mutagenic activity in two contract laboratories (Microbiological Associates, Inc. and SRI International). A standardized, sequential protocol is being used employing different concentrations of Aroclor 1254-induced rat and hamster liver S-9 preparations and the various bacterial strains. In FY 1986, results were received from these laboratories on a total of 190 test samples, encompassing 182 unique chemicals. The chemicals and the results are listed in Table 1. (Testing has been completed on a total of 1673 samples and 1355 unique chemicals since the initiation of the testing program.) Since the inception of the *Salmonella* mutagenicity testing program, the results on a total of 884 chemicals have been published or submitted for publication in the scientific literature. Detailed results for each of these chemicals can be found in references 1 to 9 at the end of the chapter.

A new contract was awarded in FY 1986 (Inveresk Research International) to provide for the testing of approximately 25 chemicals per year using protocols and *Salmonella* strains other than the ones used in the standard testing contracts. The contractor successfully completed the initial testing trial period and is testing a series of azo dyes in protocols incorporating reductive metabolism.

The mutagenicity testing of 5-(4-nitrophenyl)-2,4-pentadien-1-al (NPPD) ("Spy Dust") was completed. NPPD and two of its metabolites in rats were tested for mutagenicity in *Salmonella* and for the induction of chromosome aberrations (CAs) and sister chromatid exchanges (SCEs) in cultured Chinese hamster ovary (CHO) cells. NPPD was also tested for its ability to induce CAs and SCEs in mouse bone marrow. NPPD was mutagenic in *Salmonella*. It did not induce aberrations or SCE in CHO cells, but increased induced levels of aberrations and SCE in mouse bone marrow. The increases were not statistically significant, however. The results of these tests have been submitted for publication (reference 10 at the end of the chapter).

FY 1987 PROGRAM PLANS

In FY 1987, approximately 100 tests are scheduled to be completed in the standard *Salmonella* tests, and approximately 25 in the modified tests. Most of the chemicals to be tested will be selected from the list in Table 2. Some of these chemicals may not be tested due to unavailability, high cost, or for other reasons, while others may be added in response to NTP or other agency needs. Two new contracts will be awarded to replace the two expiring standard testing contracts. Each will provide for the testing of approximately 50 chemicals per year and will allow for the inclusion of additional *Salmonella* strains and variations in the protocol. Results from all testing will be submitted for publication. (CONTACT PERSON: Dr. E. Zeiger)

Testing the Urine of Rats for Mutagenic Activity -- As part of this project, and in collaboration with the Biometry and Risk Assessment Program, (BRAP), NIEHS, a contract was awarded (Microbiological Associates, Inc.) to test urine samples from smokers, nonsmokers, and passive smokers for mutagenicity using *Salmonella*. Before the testing began, a number of protocols were evaluated and compared with respect to ease of performance and efficiency of detection of mutagenic activity. A C18 extraction method was selected and a total of 44 urine samples were tested. The results are being analyzed by BRAP collaborators. Various protocols for testing rat urine in Salmonella were also evaluated. A protocol has been selected for use and testing of the first samples has begun.

FY 1987 PROGRAM PLANS

The results of the human urine study will be analyzed and prepared for publication. Additional chemicals will be selected and tested in the rat urine study. (CONTACT PERSONS: Dr. E. Zeiger or Ms. B. Anderson)

- In Vivo Nonmammalian Test Systems

Drosophila Mutagenesis Testing -- The sex-linked recessive lethal test, which measures both gene and chromosome mutations, and the reciprocal translocation test, which measures chromosome breakage and rejoining in *Drosophila melanogaster*, are being used in two laboratories (Brown University, Dr. S. Zimmering; and University of Wisconsin at Madison, Drs. R. Valencia and S. Abrahamson) to screen chemicals for mutagenicity. Chemicals are selected based, in part, on the basis of results obtained from previous genotoxicity tests using Salmonella and Chinese hamster ovary (CHO) cells, and in part on the basis of interest for other in vivo germ cell assays, such as the mouse specific locus test. In the standard protocol, chemicals are administered by feeding to adult males for the sex-linked recessive lethal test. If the results are negative, the test is repeated after injecting adults; if the results are again negative, the chemical is considered nonmutagenic in Drosophila for this endpoint. If the results are positive, the chemical is tested in the reciprocal translocation test using the route of administration which gave the positive result. In the reciprocal translocation test, sperm are stored to enhance the ability to recover chromosome breaks induced by the chemicals.

In FY 1986, tests were completed on 33 chemicals as shown in Table 3. Many of the samples assayed this year were tested using larval feeding as the route of administration in order to compare this procedure with others that have been used in the past. This comparison is of interest because larvae have a different array of metabolic activation enzymes than adults and may be able to activate a different set of promutagens. It has been reported that aromatic amines and polycyclic aromatic hydrocarbons (PAHs) are not readily detectable as mutagens when administered to adults. The results indicate that larval treatments are no more effective in detecting aromatic amines than adult treatments. Preliminary results suggest that mutagenic PAHs are more readily detected as being mutagenic when fed to larvae than when fed to or injected into adults.

To date, 169 chemicals have been tested in the Drosophila mutagenesis assay and many of these results are described in references 11 to 18 at the end of the chapter.

FY 1987 PROGRAM PLANS

It is anticipated that 40 samples will be tested during the fiscal year, and many of the chemicals will be selected from the list in Table 4. Many of the samples assayed this year will be tested using an assay for chromosome breakage that incorporates a DNA repair defective mutation to increase sensitivity to chemical mutagens. The results of these assays will be compared with the results obtained using the standard protocol (CONTACT PERSON: Dr. J. M. Mason)

- In Vitro Mammalian Test Systems

Mouse Lymphoma (L5178Y) Cell Mutagenesis -- The mouse lymphoma forward mutation assay at the TK locus measures mutations in a mammalian cell system. It appears that this assay has the ability to detect not only intragenic damage, but also multi-locus events.

Two laboratories (Hazleton Biotechnologies, Inc., Dr. Brian Myhr; and Inveresk Research International, Dr. Douglas McGregor) completed tests on 75 chemicals in FY 1986 (Table 5). These results represent preliminary evaluations of test data and are subject to revision; they should not be used as definitive results. Detailed results of assays for many of the chemicals tested in this system can be found in references 19 to 26 at the end of the chapter.

The laboratories have also optimized the exogenous metabolic activation system used in these studies, are analyzing the mouse lymphoma cells for their endogenous ability to activate chemicals, and are examining the relative sensitivity of different loci. Initial results of a comparative study of the relative sensitivities at the HGPRT and TK loci suggests that there is an apparent insensitivity to the mutagenic activity of chemicals at the HGPRT locus, probably because it is hemizygous and chemicals that cause lesions at the HGPRT gene and essential adjacent genes also cause cell death.

FY 1987 PROGRAM PLANS

It is projected that testing will be completed on 30 chemicals in the mouse lymphoma cell forward mutation assay. Chemicals will be selected from the listing in Table 6. In addition, cells derived from small colonies and large colonies will be examined for the stability of the translocations that have been observed on chromosome 11 in cells from small colonies. (CONTACT PERSON: Dr. W. Caspary)

Cytogenetics in Mammalian Cells -- The genetic toxicity of chemicals is indicated by increases in chromosome aberrations (CAs) and sister chromatid exchanges (SCEs). A previously validated protocol using cultured Chinese hamster ovary (CHO) cells continues to be used to measure CAs and SCEs. The sensitivity of the system to detect CAs has been found to be enhanced when allowances are made for cell cycle delay. Toxicity does not appear to contribute significantly to the induction of cytogenetic changes. Based on tests with low doses of positive chemicals or water, the resolving power of the assay system enables the detection of small increases in genotoxic effects over background. Nearly all chemicals which are positive in CA tests are also positive in the SCE tests, but the converse is not true. The cytogenetics results with 73 chemicals which have also been tested for carcinogenesis in the NTP whole animal program are being compared with those from other systems being used in CGTB. The purpose of this test will be to evaluate parameters which may be useful in predicting the carcinogenicity of chemicals. Testing of chemicals during FY 1986 was conducted by three laboratories (Environmental Health Research and Testing, Inc., Dr. D. Gulati; Hazleton Biotechnologies, Dr. J. Ivett; and American Biogenics, Dr. K. Loveday).

Testing was completed on 63 chemicals in FY 1986. Results are presented in Table 7. These results represent preliminary evaluations of test data, are therefore subject to revision, and should not be used as definitive results.

FY 1987 PROGRAM PLANS

Testing of chemicals will proceed at a rate of approximately 100 chemicals per year among the three laboratories. Chemicals will be chosen from the list in Table 8. A description of the test protocol and supporting data from control experiments as well as an in-depth statistical analysis to determine the power of the system have been published. Results with over 150 chemicals are being published. (CONTACT PERSONS: Dr. E. Zeiger, Dr. M.A. Resnick, and Dr. M. Shelby)

- In Vitro Multiple Test Systems

Coordinated Testing Project -- A major component of this project has been the recent retrospective evaluation of the genetic toxicity of the 73 chemicals which were identified as carcinogens or noncarcinogens in the NTP rodent carcinogenesis assay. The main thrust of the project has been to test these 73 chemicals in the four tests which comprise the Class I and Class II categories (defined below) of genetic toxicity tests.

Class I: Gene mutations in bacteria (Salmonella)/microsome assay) and in mammalian cells (L5178Y mouse-lymphoma cell TK$^{+/-}$ forward mutation assay).

Class II: Chromosome effects in mammalian cells: The in vitro cytogenetics assay in Chinese hamster ovary (CHO) cells for detection of chromosome aberrations and sister chromatid exchanges.

The testing of the 73 chemicals has been completed; the test results are currently undergoing analyses and evaluation prior to being submitted for publication.

Another 30-40 chemicals, which have been subsequently completed in the rodent carcinogenesis assay through the peer review process and which have been reported out by the NTP, will be subjected to a similar evaluation in an exercise to validate the results of the first data set of the 73 chemicals.

Class III: Mammalian cell transformation assays: None of these assays have been developed adequately for use in testing coded chemicals on a routine basis so are no longer being used in this project.

Class IV: DNA damage/repair:

a. The *in vitro* unscheduled DNA synthesis (UDS) in rat liver primary *cell culture* assay.

The induction of excision DNA repair, measured as unscheduled DNA synthesis (UDS) in non-dividing hepatocytes, has been shown to be a useful indicator of the genetic toxicity of chemicals. The endpoint of the assay, the detection of H3-thymidine incorporation into DNA by silver grain analysis using an autoradiographic technique, is relatively insensitive, however, so that extensive repair must occur before chemical activity can be detected.

Nearly 120 chemicals have been evaluated in the assay which was performed under contract. The results from testing a subset of 44 chemicals in a retrospective study indicated that the assay did not have any advantage over several other short-term genetic toxicity assays (Class I and II) in detecting or discriminating between rodent carcinogens and noncarcinogens that were identified in the NTP rodent carcinogenesis assay. In no case did the *in vitro* UDS assay detect a carcinogen that was not detected by *three or more* of the other genetic toxicity endpoints which were being compared in the retrospective study. The *in vitro* UDS assay exhibited very high specificity and positive *predictivity*, but the sensitivity and negative predictivity for the subset of chemicals was lower than that for the other *in vitro* short-term assays.

It was concluded from these results that, for the purposes of the NTP short-term genetic toxicity testing program, it was inappropriate to continue using the *in vitro* UDS assay for purposes of screening chemicals. The *contract, therefore*, has been terminated. The test results are being evaluated and prepared for publication. In consideration of any new contract, the focus will be on how to use the *in vitro* UDS assay to identify genotoxic hepatocarcinogens *among selected* chemicals of interest to the NTP.

b. The *in vivo - in vitro* unscheduled DNA synthesis (UDS) rat (rodent) liver *primary cell culture* assay.

The *in vivo - in vitro* unscheduled DNA synthesis (UDS) assay can *provide information on* important *in vivo* factors related to route of administration, metabolic *activation* and detoxification, and other aspects of chemical disposition. Since this assay can be performed in different rodent species, e.g., rats, mice, hamsters etc., responses to chemical activity in the *in vivo - in vitro* UDS assay can be compared to the differences *in patterns of tumor* induction that may occur for any particular chemical among the two sex/species utilized for the NTP carcinogenesis assay.

A small but representative group of rodent hepatocarcinogens were tested in the in vivo - in vitro hepatocyte UDS assay using the same sex/species in which the hepatocarcinogens had been identified. None of these chemicals induced detectable in vivo DNA damage/repair, though one-half of the chemicals exhibited genetic toxicity in several in vitro short-term tests. However, nearly all of the chemicals did induce scheduled DNA synthesis (S-phase) a pre-proliferative response which is an indicator of hepatotoxicity.

The contract under which these studies were performed has expired. However, it is in the interest of the NTP to continue to evaluate hepatocarcinogens and other selected chemicals in more comprehensive studies using these and other in vivo endpoints that are indicators of genetic and cellular toxicity. It is the intention of the NTP to pursue these studies under a new contract.

FY 1987 PROGRAM PLANS

It is planned to evaluate up to 40 additional chemicals for genetic toxicity in the retrospective study in each component of the Class I and Class II categories of in vitro short-term tests. Further development and the comprehensive testing of selected chemicals in the in vivo - in vitro UDS rodent hepatocyte assay and other endpoints for genetic and cellular toxicity will be pursued under a new contract. (CONTACT PERSON: Dr. J.W. Spalding)

- Data Systems and Their Utilization

Genotoxicity Data Evaluation and Analysis -- Studies over the last 10-15 years have indicated that most chemical carcinogens exhibit genetic toxicity. Genetic toxicology data from the Cellular and Genetic Toxicology Branch (CGTB) and the associated literature is incorporated into the Introduction of the NTP Toxicology and Carcinogenesis Technical Report and the carcinogenicity of the various chemicals is discussed in terms of their response in these mutagenicity assays. Presentation of the CGTB's genetic toxicology data includes data tables on Salmonella, in vitro cytogenetic, Drosophila, mouse lymphoma, unscheduled DNA synthesis (UDS), and in vitro transformation assay results. This information was included in 19 NTP Technical Report final drafts in FY 1986. The chemicals were: ampicillin trihydrate, boric acid, bromodichloromethane, chlorpheniramine maleate, 1,4-dichlorobenzene, dimethylmethylphosphonate, dimethylvinyl chloride, 1,2-epoxybutane, ethylene oxide, hexylresorcinol, methyl carbamate, methyl methacrylate, oxytetracycline hydrochloride, pentachloronitrobenzene, phenylephrine hydrochloride, rotenone, tetrakis-(hydroxymethyl) phosphonium chloride and sulfate, trichloroethylene and xylenes. Galley and precamera versions of earlier reports were also proofed with substantial revisions made for the genetic toxicology statements in the discussion section of 3-chloro-2-methylpropene.

Reviews of genetic toxicology data were prepared for the NTP Toxicology Design Review Committee on coconut diethanolamide, 1,2-dichlorobenzene, lauric acid diethanol condensate and oleic acid diethanolamine. Assistance was also provided in the review and summarization of cytogenetic data on 24 compounds included in a special CGTB study.

FY 1987 PROGRAM PLANS

Methods for report development and tracking are becoming increasingly computer assisted and more efficient. Coordination of activities related to CGTB contributions to the NTP Technical Reports is expected to continue at the current level with greater attention given to compilation of information packages for the Toxicology Design Review Committee. (CONTACT PERSON: Dr. J. B. Bishop)

Environmental Mutagen Information Center (EMIC) File -- The Environmental Mutagen, Carcinogen, and Teratogen Information Program, which receives funding from the NTP, collects, organizes, and disseminates primarily published information on chemicals tested for mutagenicity, and maintains the EMIC computerized data file. Located since its inception in 1969 at the Oak Ridge National Laboratory (ORNL), the EMIC file contained as of July 1986, 60,158 records on over 20,000 unique agents, 49,721 of which are available on-line from TOXLINE (at the NLM) and 58,111 from RECON (at the ORNL). Each record contains bibliographic information, assay systems, and key words defining agents tested and organisms studied. (CONTACT PERSON: Mr. S. Stasiewicz, NIEHS)

TEST METHODS DEVELOPMENT AND VALIDATION PROJECTS

• In Vitro Assays

Mammalian Cell Transformation -- Contracts supporting evaluation of three assay systems -- Syrian hamster embryo (SHE) cell primary cultures, SHE cells infected with Simian adenovirus (SA7), and rat cells infected with murine retrovirus (Rauscher (RLV)) -- were completed. Results describing studies on identified and coded chemicals within and between the systems have been reported (references 27 to 32 at the end of the chapter).

The overall results derived from this project suggest that these systems, and the Balb/c 3T3 system which had been evaluated previously, generally demonstrate a good degree of intra- and inter-laboratory reproducibility. However, none of the assays have been developed adequately for use in testing coded chemicals on a routine basis. These systems, which each may function through different mechanisms, nevertheless, are the most proximate in vitro surrogates of induced neoplastic processes in vivo. Their continued use in the study of chemical induced neoplasias should be useful. (CONTACT PERSON: Dr. R. W. Tennant)

Yeast Aneuploidy Test System -- Aneuploidy contributes significantly to the genetically based disease burden in human populations, and somatic aneuploidy has been implicated as a cause of cancer induction. A yeast system has been developed which can detect chromosome loss in mitotically growing cells and chromosome gain in mitotic or meiotic cells. This system is being used to genetically distinguish agents which primarily cause aneuploidy as compared to those which induce both aneuploidy and specific chromosomal DNA changes such as recombination and mutation and may be detected in other test systems. The work is being done in the laboratories of Dr. Seymour Fogel, University of California at Berkeley, and Dr. Fritz Zimmermann, Technische Hochschule, Darmstadt, Federal Republic of Germany.

The chromosome loss portion of the system has just undergone the final stages of extensive validation in terms of reproducibility of negative and positive controls. Tests are nearly complete on the 19 coded compounds tested in both of the laboratories. Preliminary work with uncoded compounds has shown that several solvents cause aneuploidy and that for some of these there is considerable enhancement by a brief cold shock of between 0 and 20 degrees; the optimum temperature varies depending on the chemical.

FY 1987 PROGRAM PLANS

Approximately 30 chemicals per laboratory will be tested under code for the ability to induce chromosome loss. In addition validation will begin on the mitotic and meiotic chromosome gain portion of the system using approximately 15 chemicals. As part of the development portion of this work, efforts are being directed to the construction of a genetic system that will allow the detection of both chromosome gain and loss in one strain. Aneuploidy will be analyzed genetically and molecularly to evaluate the effects of chemicals on single chromosomes vs. several chromosomes. It has been found that selection of an aneuploidy event for one chromosome is frequently associated with aneuploidy for additional chromosomes. Using gel procedures that enable the display of all the chromosomes, it should be possible to evaluate the genomic effects of chemicals. (CONTACT PERSON: Dr. M. A. Resnick)

Response of Centromeres to DNA Damaging Agents-- The purpose of this project with Dr. K. Bloom, University of North Carolina is to develop detailed information on: a) the interaction of DNA damaging agents with the centromere essential region (CEN) and surrounding region of several chromosomes in yeast, and b) the repair processes involved in modifying the damage. This project will also enable an assessment of the ability to induce DNA damage in relationship to chromosome structure because of the unique and ordered structure of centromeres in yeast.

FY 1987 PROGRAM PLANS

In the early phases of this work, which is to start at the beginning of FY 1987, cellular and purified centromere DNAs of chromosomes are to be examined for their susceptibility to DNA damaging agents. A plasmid system, currently under development inhouse, will allow a large number of a plasmids with a particular centromere to exist in the cell. This system will be used to assess differences between centromeres on plasmids vs. chromosomes in susceptibility to DNA damage and repair. If they are comparable, the plasmid system will greatly enhance the ability to assess events inside the cell. (CONTACT PERSON: Dr. M. A. Resnick)

Assays for Tumor Promoters -- Some carcinogenic chemicals are not detected in currently available short-term genetic toxicity assays and, therefore, are presumed to act by nongenetic mechanisms. Because of the potential role of these chemicals in causation of human cancer, there is a need to develop cell culture systems which can be used to identify such chemicals and elucidate their mechanism(s) of action. One such cell culture system, the V79 metabolic cooperation assay, is continuing to be studied as a joint NTP/NIOSH project.

FY 1987 PROGRAM PLANS

NTP chemicals with known F344 rat and $B6C3F_1$ mouse carcinogenesis data, as well as known responses in various short-term assays, will continue to be analyzed for activity in the V79 metabolic cooperation assay. Inter- and intra-laboratory variations in responses to test chemicals are being evaluated. During this year, the activities of chemicals in the metabolic cooperation assay will be analyzed with reference to the genotoxicity/nongenotoxicity of the selected carcinogens and noncarcinogens. The outcome of these studies should be useful in determining whether the V79 metabolic cooperation assay will supplement short-term *in vitro* tests currently used by the NTP. (CONTACT PERSON: Dr. R. J. Langenbach)

Development of Human Cell Assay Systems for Genetic Toxicity -- Species differences in response to chemical carcinogens are known to exist and therefore the evaluation of a chemical's genetic effects in human cells may be more relevant to human health hazard than effects in rodent cells. However, human cell systems for use in genetic toxiciology have received less attention than rodent cell systems and, therefore, further basic development of human cell systems is needed. Furthermore, both rodent and human cells *in vitro* have different metabolic capabilities than existed in these cells *in vivo*, and studies are needed to have both cell systems better mimic *in vivo* metabolism. Dr. S. Strom of Duke University is investigating the use of freshly prepared human hepatocytes for metabolic activation and human fibroblasts as genetic target cells. Two other contractors, Dr. C. Crespi of Gentest and Dr. D. Kaufman of the University of North Carolina (UNC), are working to develop human cell systems and concommitantly improve metabolic activation capability of the cells. The goal is for chemical activation and measurement of genetic endpoints to occur in the same cell system.

FY 1987 PROGRAM PLANS

At Duke University, freshly isolated human hepatocytes (from surgery or organ donors) are used for metabolic activation, and human fibroblasts are used for measurement of the genetic endpoints. The endpoints measured are unscheduled DNA synthesis (UDS) in hepatocytes, and gene mutations and SCEs in the fibroblasts. HPLC analysis of test chemical metabolites is also being conducted. Standard chemicals used are 2-acetylaminofluorene, aflatoxin, benzo(a)pyrene, and dimethylnitrosamine. Inter-individual variation in carcinogen activation by hepatocytes from different donors is being measured. Methodologies for storage of hepatocytes will be developed so that hepatocytes from the same donor can be used repeatedly. In addition, comparisons between human and rodent hepatocytes for metabolic activation levels and between human fibroblast and hamster V79 cells as genetic targets are being made.

The second approach (Gentest and UNC) involves improving the metabolic capability of human cell systems so that they can be used for genetic toxicology screening. Hybridization of metabolizing cells (freshly prepared hepatocytes or liver cell lines) with low metabolizing target cells and chromosome transfer are being conducted at UNC to improve cellular metabolism. In the UNC contract, cytofluorimetric measurement of cytotoxicity and genotoxicity, mutation of the lambda immunoglobin, and DNA repair are being developed as endpoints in human lymphoblasts.

At Gentest, transfection of a cloned P450 gene via a plasmid and/or viral vector into human lymphoblasts is being pursued to improve the cell's metabolic capability. Chromosome transfer and selective cloning after mutagen treatment will also continue in an attempt to obtain clones with improved metabolic capability. The endpoints measured in the human lymphoblast are gene mutation at the TK and HGPRT loci, aneuploidy and chromosome aberrations. (CONTACT PERSON: Dr. R. J. Langenbach)

- In Vivo Mammalian Somatic Cell Test Systems

Mouse Bone Marrow Cytogenetics -- This short-term, in vivo test system offers an efficient method for assessing the in vivo genetic activity of NTP test chemicals. The primary objectives of this study are to test chemicals for their ability to induce cytogenetic damage in the same strain of mouse, the $B6C3F_1$, used in NTP chronic toxicity studies and to better define the role of this assay in the overall assessment of chemical toxicity.

Both laboratories engaged in this project (Brookhaven National Laboratory, Dr. R. Tice; and Oak Ridge Associated Universities, Dr. A. McFee) have committed the majority of their efforts in FY 1986 to the testing of chemicals for cytogenetic effects in the bone marrow.

Three test chemicals of particular interest were nitrophenyl pentadiene aldehyde ("spy dust"), methylisocyanate (MIC) and 1,3-butadiene. Manuscripts reporting the results of tests on these three are being submitted for publication. As part of the CGTB short-term test validation exercise involving 73 chemicals for which two-year NTP toxicology and carcinogenesis studies were recently completed, 16 of these chemicals were tested in the in vivo cytogenetics assay. These results were presented at a Branch workshop held at NIEHS in May 1986.

FY 1987 PROGRAM PLANS

The primary objective is to concentrate testing on the remainder of the 73 chemicals being studied by the Branch. To achieve this, testing capacity has been increased from 24 to approximately 40 chemicals per year. Because test results on a limited number of the chemicals indicated the in vivo assay offered an important complement to short-term in vitro tests, major effort will go into defining the performance and role of the in vivo cytogenetics assay in predicting potential carcinogenicity. As a part of this effort, interaction with statisticians at NIEHS has been initiated to refine and improve methods for data analysis. (CONTACT PERSON: Dr. M. Shelby)

Mouse Erythrocyte Micronucleus Assay -- Micronuclei are chromatin-containing cellular inclusions that have their origin in broken chromosomes or disrupted mitoses, and, as observed in anucleate erythrocytes, have been utilized for several years as the basis for determining the genotoxicity of chemicals in intact rodents. Through a project with Dr. James MacGregor at the USDA Western Regional Research Center, the utility of the mouse peripheral blood micronucleus assay continues to be investigated. Blood smears obtained from mice in NTP sponsored prechronic studies are received and scored on a routine basis. Blood smears from over 20 studies have been scored or are in the process of being scored.

To assess the capacity of the mouse bone marrow micronucleus assay to discriminate between carcinogen-noncarcinogen pairs of structural analogs, both of which exhibit genetic toxicity in vitro, three pairs of chemicals have been tested. Results with 4-chloro-o-phenylenediamine and 4-nitro-o-phenylenediamine have shown the former, a carcinogen, to be clearly positive and the latter, a noncarcinogen, negative. Data from two other pairs, o-toluidine/o-anthranilic acid and 3-chloromethylpyridine/2-chloromethylpyridine are still being analyzed.

In a study specifically designed to determine the response of the micronucleus assay to known genotoxic carcinogens under prechronic exposures, triethylenemelamine and urethane were administered to mice in drinking water for 90 days and micronuclei are being scored in bone marrow and in polychromatic and normochromatic erythrocytes from the peripheral blood. The dose-related induction of micronuclei in the peripheral blood of 1,3-butadiene-exposed mice was demonstrated using blood smears from 14-day and 90-day studies.

FY 1987 PROGRAM PLANS

Blood smears from prechronic studies will be scored as they become available. Publication of all results from prechronic studies is planned. A major initiative in FY 1987 will involve studies to determine if the bone marrow micronucleus assay can be used as a primary screen for in vivo genetic toxicity in place of the standard cytogenetics assay now employed, the former being a far more economical test. This effort will involve the conduct of bone marrow micronucleus tests on the chemicals from the 73 being studied by the Branch for which two-year rodent data are available and on which cytogenetic data are or soon will be available. (CONTACT PERSON: Dr. M. D. Shelby)

Human Lymphocyte Cytogenetics -- The measurement of chromosomal damage in peripheral lymphocytes offers a practical means of detecting exposures of humans to genotoxic agents. Differences in protocols used in cytogenetic studies on persons exposed to chemical agents have often precluded cross comparison of results. Information obtained with a standardized protocol will be useful in the design and interpretation of future cytogenetic studies of populations exposed to potential chromosome-damaging agents.

Two laboratories (Brookhaven National Laboratory, Dr. M. Bender; Oak Ridge National Laboratory, Dr. J. Preston) have completed scoring the frequencies of chromosome aberrations (CAs) and sister chromatid exchanges (SCEs) in lymphocytes of approximately 480 individuals using a standardized protocol. This study group includes about 400 individuals from the Brookhaven National Laboratory work force selected by a stratified, random sampling scheme, 60 Brookhaven retirees over the age of 65 and a few individuals under the age of 20. This last group of healthy youths is being expanded through collaboration with the Department of Pediatrics at a nearby medical school. At this point in the analysis of the data, the only factors that have been identified as significantly affecting SCE are smoking and sex, with females and smokers having significantly higher frequencies of SCE, than males and non-smokers, respectively. None of the factors studied have shown an effect on CAs.

FY 1987 PROGRAM PLANS

Sampling and scoring will be completed on the under-20 age group. Data analysis and publication of results will be given high priority. (CONTACT PERSON: Dr. M. D. Shelby)

- Gene Transposition Assays

Chemically Induced Transposition in Drosophila -- It has been demonstrated in Drosophila that a large proportion of apparently spontaneous mutations, including mutations recovered from natural populations, are the result of insertion of transposable elements. Transposition of these elements is very rare, however, under normal laboratory conditions. It is not known to what extent transposition is a cause of spontaneous mutation in mammals, or to what extent exposure to chemicals induces transposition. A contract (University of Kentucky, Dr. C. Osgood) was designed to answer the latter question in Drosophila and, if chemicals were found to induce transpositions, to design and develop an assay for chemically-induced transposition to be used as part of the Cellular and Genetic Toxicology Branch mutagen screening program.

Three different methodologies have been developed to assay for transposition. In the first, forward mutations in cloned genes can be analyzed at the molecular level for insertions of transposable elements. In the second, reversions of mutations known to have resulted from transposon insertion can be examined for excision of the resident transposon. In the third, a genetically marked transposable element can be followed as it moves from one chromosome to another. Use of the first two methodologies to assay for chemically-induced transposition have produced mainly negative results. This work has resulted in two publications (references 33 and 34 at the end of the chapter).

FY 1987 PROGRAM PLANS

A contract will be awarded to use the third methodology in an assay for chemically-induced transposition. (CONTACT PERSON: Dr. J. M. Mason)

Mouse Endogenous Retroviral Long Terminal Repeat (LTR) Elements for Studying Gene Transposition in Environmental Carcinogenesis -- Continuing studies on endogenous mobile repeat LTR (MRL) containing elements (Mbo-I repeats) were conducted through an Interagency Agreement with the Department of Energy at the Oak Ridge National Laboratory (Dr. W. K. Yang, Principal Investigator). Recent studies have revealed that the MRL sequences are preferentially expressed in mature reproductive organs of both male and female mice. The results indirectly indicate that these elements are more likely to transpose in the germ-line of the mouse. The current research effort is concentrating on examining their possible role in germ-line mutagenesis induced by chemical mutagens. Other studies reveal that neoplastic cells of mice contain activated murine leukemia virus-related proviruses. These sequences represent a distinct family of retrotransposable elements in the mouse. In the case of NIH-3T3 cells transformed by 5-azacytidine (cells are tumor forming in mice), there is characteristic expression of these elements as messenger mRNAs distinct from those known for exogenous murine leukemia viruses.

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Experiments are in progress to test the functional response of LTRs to chemical carcinogens by constructing recombinants of the LTR under study with the *ras* oncogene and subsequent transfection of mouse cells *in vitro*. These studies may provide for development of an assay method for non-mutagenic carcinogens. (CONTACT PERSON: Dr. R. W. Tennant)

- Special Application

Mutagens Formed From the Cooking of Foods -- The mutagens formed during the frying or boiling of beef have been extensively characterized with respect to their mutagenicity in *Salmonella*, and to a lesser extent in cultured mammalian cells and rodent bone marrow. All the chemicals are mutagenic in *Salmonella*, and the contribution of each mutagen to the overall mutagenicity of fried ground beef and boiled beef extract has been determined. The mutagenic and clastogenic activities of these mutagens in cultured mammalian cells were in inverse proportion to their mutagenicity in bacteria. The clastogenic activity of the mutagens in mouse bone marrow paralleled their activity in cultured mammalian cells. Studies underway support the conclusion that during frying of ground beef, the low molecular weight components of the meat responsible for mutagen formation are transported to the surface of the meat where they react at high temperature to form mutagens. If these low molecular weight components are removed by brief heating in a microwave oven, mutagens are not formed when the beef is subsequently fried.

Preliminary studies with boiled beef have shown that some of the mutagens reported by other laboratories may be the result of artifacts in the laboratory cooking procedures.

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Additional mutagens will be tested in cultured mammalian cells and mouse bone marrow as sufficient quantities are synthesized. Through the use of radiolabelled mutagens, the types and levels of DNA adducts are being measured, and limited *in vitro* metabolism and *in vivo* pharmacokinetic studies will be performed. Studies will be initiated to characterize cooking conditions or identify additives that will prevent or minimize mutagen formation. (CONTACT PERSON: Dr. E. Zeiger)

- Heritable Effects - Mammalian Assays

Mouse Morphological Specific Locus Study -- Exposure of humans to mutagenic chemicals poses the potential risk of induced mutations in germ cells. The morphological specific locus method is, at present, the most practical and reliable means available in mammals for detecting induced heritable gene mutations.

The two basic objectives of this project (Oak Ridge National Laboratory, Dr. L. Russell) are to investigate chemically-induced mutation processes in mammalian germ cells using N-ethyl-N-nitrosourea (ENU) as a model mutagen, and to test chemicals for mouse germ cell mutagenicity. The test employs two strains of mice to detect mutations at seven loci that affect visible characteristics (coat color, eye color, and ear shape).

Studies completed this year with platinol and urethane have demonstrated that neither of these compounds induces specific locus mutations in either spermatagonial or postspermatagonial cells. No mutants have been found among 17,112 offspring from male spermatagonial stem cells treated with acrylamide; however, one (1) mutant was found among 10,717 offspring derived from post spermatagonial cells treated with acrylamide. Investigations of the effect of age of males at the time of treatment with ENU upon the mutation rate indicated no significant difference between 14-day-old animals and adults.

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Further tests of offspring from post-spermatagonial stem cell stages treated with acrylamide will be conducted. Molecular dosimetry experiments with ^{14}C-labeled acrylamide are also planned to characterize its binding to macromolecules within mouse germ cells. Unscheduled DNA synthesis (UDS) studies on platinol will be conducted to determine if it reaches the testes. An experiment to investigate the possible protective role of follicle cells against ENU induction of mutations in eggs of female embryos treated *in utero* will be completed. Specific locus tests will be initiated on three new chemicals, including adriamycin and chlorambucil. (CONTACT PERSONS: Dr. M. D. Shelby or Dr. J. B. Bishop)

Mouse Heritable Translocation Testing -- Heritable translocations resulting from the exchange of segments between non-homologous chromosomes are known to result in serious human diseases such as Down's and *cri du chat* syndromes. The purpose of this study (Oak Ridge National Laboratory, Dr. W.

Generoso) is to assess the ability of chemicals to induce heritable chromosomal damage in mouse germ cells. Dominant lethal effects and effects on reproductive capacity are determined prior to conducting heritable translocation tests.

Final analysis of data from females treated with hexamethylphosphoramide confirmed a weak dominant lethal effect in first litters. Acrylamide, previously found to be a potent inducer of dominant lethality, was shown to induce heritable translocations in male mice. Ethylene oxide, previously shown to induce dominant lethal mutations in postmeiotic germ cells of male mice with a demonstrable dose rate effect, was tested for induction of heritable translocations and a dose related increase was observed in each of two stocks exposed by inhalation to doses from 165 ppm up to 300 ppm. In continuing work on the effects of germ cell mutagens in treated females, morphological abnormalities have been observed among both the dead and surviving fetuses of females exposed to inhaled ethylene oxide at the time of fertilization or during the early pronuclear stage of the zygote.

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Tests for induction of dominant lethal mutations in male germ cells will be conducted on adriamycin, bisacrylamide, chlorambucil and platinol. Heritable translocation tests will be initiated when dominant lethal tests are positive. Dominant lethal test on zygotes after one to six hour postmating treatment with acrylamide, adriamycin, bisacrylamide, ethylene oxide, ethyl methanesulfonate, ethylnitrosourea and mitomycin C are also planned or in progress. Chromosome analysis of embryos treated with ethylene oxide as zygotes one to six hours postmating will be conducted to investigate a possible genetic basis for the observed congenital abnormalities. (CONTACT PERSONS: Dr. M. D. Shelby or Dr. J. B. Bishop)

Mouse Biochemical Specific Locus Study -- The biochemical specific locus assay offers a second animal model with which to investigate the ability of chemicals to induce heritable mutations in mammalian germ cells. This assay has two particularly desirable features. First, the assay detects changes in specific enzymes or proteins which offers the opportunity to relate chemically-induced mutations to changes in enzyme structure and function. Second, the potential availability of a large number of loci for analysis means that more information can be obtained from each F_1 animal than in the morphological specific locus test.

The objectives of this study (Research Triangle Institute [RTI], Dr. S. Lewis) are to investigate mutagenesis processes in the germ cells of male and female mice using N-ethyl-N-nitrosourea (ENU) and ionizing radiation as model mutagens and to test a limited number of chemicals for germ cell mutagenicity.

The number of control loci scored during the past year exceeded 100,000 to bring the number of total historical control loci to more than 825,000. A mobility variant of nucleoside phosphorylase was found in the control group.

If proven to be a mutant, it will constitute the second spontaneous mutant recovered to date.

Experiments have been initiated to assess the effects of x-rays upon male and female germ cells. No presumptive mutants have been recovered thus far from a relatively small population of 399 offspring of C57BL/6J females treated with 300 rad. Two presumptive mutants have been recovered from treatment of male spermatagonia with 600 rad. This electrophoretic mutation test has also been used to evaluate the potential of ethylene dibromide (EDB) to induce mutations in spermatagonia. No mutations were detected in 1409 offspring screened from parent male DBA mice treated with 100 mg/kg EDB.

Of the new loci now being examined through use of isoelectric focusing of blood proteins, four mutations have been found at two of these loci; three mutations have been found at the carbonic anhydrase-2 (*Car-2*) locus and one at the transferrin locus. One of the *Car-2* mutants may provide an animal model of a newly described human disease involving deficiency of carbonic anhydrase. Molecular and clinical collaborations have been established. A molecular biology laboratory was set up at RTI to characterize spontaneous and induced mutations in mice.

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The mobility variant of nucleoside phosphorylase found in the control group is being screened to determine if it was newly arisen or originated in the parental C57BL/6J or DBA/2J stocks. Progeny from male late germ cell stages exposed to 600 rad will be evaluated. The effects of 300 rad upon female germ cells and the response of late male germ cells to 300 rad will also be investigated. The mutagenicity of one additional chemical will be tested in the system. (CONTACT PERSONS: Dr. M. D. Shelby or Dr. J. B. Bishop)

- (Collaborative Activities

Collaborative Study on Short-Term Tests -- The NTP was represented on the *ad hoc* Working Group that directed the International Program on Chemical Safety's (IPCS's) two collaborative studies on the Application of Short-term Tests to Predict Mutagenic and Carcinogenic Potential. The results of the study on *in vitro* tests were published in 1985 by Elsevier as Volume 5 of *Progress in Mutation Research*. The second study, which involved the use of short-term *in vivo* tests for genetic toxicity, was completed in 1985. All chapters for a book have been submitted, reviewed and edited and are ready for publication as soon as IPCS reaches an agreement with a publisher.

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The IPCS will contract to have the results of the *in vivo* study published. (CONTACT PERSON: Dr. M. D. Shelby)

INTRAMURAL RESEARCH PROJECTS

Recombination, DNA Repair and Centromere Damage in Yeast -- The purposes of this research program are as follows: (1) to characterize the mechanisms of DNA repair in the yeast *Saccharomyces cerevisiae*; 2) to determine the importance of chromosomal structure on the induction and repair of DNA damage, particularly in centromeric regions; 3) to determine the role of DNA repair mechanisms in the process of normal meiosis and in dealing with external insults during meiosis; and 4) to understand various mechanisms of recombination.

The induction of DNA damage is expected to be dependent on chromosomal structure. Protein associations, folding, and extent of superhelicity of DNA within chromosomes could influence the induction and distribution of damage. Because of the role that centromeres play in chromosome segregation and the unique structure of the protein-DNA complex, we are examining the distribution of damage in the centromeric region of chromosomal DNA. In terms of single-strand damage, the centromere sequence from cells exhibits a somewhat different pattern of UV-sensitivity to that of purified DNA irradiated *in vitro*. There are a significant number of lesions on opposite strands that are sufficiently close so as to lead to double-strand breaks when the DNA is treated with UV-endonuclease. In spite of the large of amount of damage induced in the centromere, aneuploidy is not detected, which suggests that the damage may be dealt with in a unique fashion.

Several repair mutants are being examined in meiosis. Genes required for the mitotically defined double-strand break repair pathway are essential for normal meiosis, while the excision repair genes are not. Cells lacking the *RAD52*, *-50*, or *-57* gene products die in meiosis. Using procedures we have *developed* for determining the stability of recombinational events during (as opposed to the conclusion of) meiosis, we have established the genetic order of function as *50*, *52*, and *57*. These results correlate with changes that occur in the DNA of the mutants during meiosis. The *rad50* mutants are blocked early in meiosis and exhibit no breaks in chromosomal DNA. The *rad52* mutants accumulate approximately 200-400 single-strand breaks and the *rad57* mutants exhibit both single-strand and a small number of double-strand breaks.

The enzymes involved in recombination and repair are expected to include nucleases and also proteins directly involved in strand transfer. We have identified an alkaline deoxyribonuclease that is lacking in *rad52* mutants and is implicated in recombination. Since the nuclease has been purified to homogeneity and the structural gene now appears to be cloned, it will be possible to determine the role of this gene and enzyme in recombination, repair and mutagenesis.

New approaches have been taken for examining the genetic control and mechanisms of recombination in mitotic and meiotic cells. A unique system has been developed for analyzing and isolating mutants in the SCE process. Using this system we have shown that several of the genes required for homologous chromosome recombination are also involved in SCE and that the centromere appears to effect SCE. Two categories of mutants have been isolated, those which enhance and those which depress spontaneous SCE. Among the enhanced SCE mutants are those which are not involved in repair; they may function directly in replication.

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To investigate genetically the effects of damage in the centromere, we are developing centromere containing plasmids which allow the selection of altered centromeres. The system has enabled us to show that cells can tolerate a large number of extra centromeres and to investigate factors that may be involved in centromere segregation. In experiments with meiotic cells, our preliminary results suggest that the breaks we observed in the rad52 mutants may be at unique sites, indicating that they have an important role in recombination. We are attempting to identify and characterize these sites. Nucleases and proteins involved in DNA strand exchange are being investigated using antibodies to repair and recombination proteins in other systems as well as by direct isolation. The mutants will be important for determining common and unique functions in various types of repair and recombination. We are presently cloning the corresponding genes. (CONTACT PERSON: Dr. M. A. Resnick)

Molecular Genetics of Meiosis and Mutagenesis in Yeast -- A model test system has been constructed in the yeast, *Saccharomyces cerevisiae*, using a cloned tRNA gene on a genetically engineered mini-chromosome which allows direct DNA sequence determination of the spectrum of molecular changes occurring in the target DNA following mutagenic challenge. The DNA sequence of 50 spontaneous mutants has been determined and is being extended to compile the background spectrum of spontaneous mutation in this system. This spontaneous spectrum shows a continuous distribution of phenotypically expressed mutations in the coding region of the gene. Ultraviolet radiation induced mutations have been induced and the mutated genes are being sequenced in order to determine the consequences of radiation induced mutagenesis at the molecular level in a eukaryotic cell. This SUP4-o system is being developed as a rapid genetic test for the induction of all types of mutation occurring within a eukaryotic gene which will also allow determination of the mutagenic specificities of chemical agents giving positive responses.

A combined functional and structural analysis is in progress to identify and analyze the cellular functions which are required for meiosis in yeast. In particular, we are focusing on the SPO11 gene which is required for recombination and proper chromosome segregation during meiosis.

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The structural organization and functional role of specific structures in differentiating meiotic cells have not yet been fully determined. Methods of isolation and identification by light and electron microscopy have been developed for meiosis specific structures in yeast. These methods in combination with immunofluorescence have demonstrated that meiotic chromosome behavior in yeast is similar to that previously observed in the mouse and other mammals, including humans. We are attempting to extend this methodology to a structural analysis of the protein components of meiosis specific structures such as the synaptonemal complex which have been implicated in proper chromosome behavior. Such an analysis will be used to characterize mutants which are defective in meiotic DNA metabolism. This fundamental information is necessary for an understanding of the structural elements which are required for proper DNA metabolism and chromosome stability during meiosis and the differentiation of germ line cells. (CONTACT PERSON: Dr. C. Giroux)

Mammalian Cell Molecular Genetics -- The molecular genetics group is concerned with the role of endogenous proviral sequences and related transposable elements and oncogenes in spontaneous and induced leukemias of the mouse. The Fv-1 gene is one of the most important genetic factors influencing retroviral leukemogenesis in the mouse. During the past year our study has involved constructing retroviral packaging mutants by recombinant DNA techniques. Such mutants are not infectious but are capable of forming virions containing a retroviral vector genome. The packaging mutant will contribute Fv-1 sensitivity and the selectable marker (neomycin resistance) of the vector will be used as a measure of successful integration.

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Plans include continuing our recently initiated study of the molecular mechanism by which the mouse Fv-1 gene blocks retrotransposition. Experiments will be designed to demonstrate the nature of the interaction between the Fv-1 gene product and the virion target. A scheme for molecular cloning of the Fv-1 gene has also been developed which involves insertion mutagenesis in heterozygous Fv-1 NB mice. In addition we will continue efforts to identify putative oncogenes activated by provirus integration in the RFM/Un mouse reticulum cell sarcoma. Our previous work has demonstrated somatically acquired provirus in reticulum cell sarcomas and it is speculated that they are integrated in regions of the genome important in the oncogenic process.

Plans for 1987 also include a study of the activation of proviral gene expression by nonmutagenic carcinogens. This study will focus on the possibility that these compounds influence gene expression. An assay system is being developed which allows for marker selection from cells with activated provirus.

A final project for the coming year involves transformation of cells in culture by a variety of viral oncogenes in the presence and absence of helper virus. These experiments are designed to further investigate the requirement for multiple oncogenes in transformation of primary cells. (CONTACT PERSON: Dr. L. R. Boone)

Salmonella Mutagenesis Research -- The role of free radicals in mutagenesis of *Salmonella* by sodium bisulfite and glutathione has been studied. Sodium bisulfite autooxidizes in solution to form a series of sulfite and sulfate free radicals. Substances or treatments which slow the autooxidation rate enhance the mutagenicity, leading to the conclusion that rapid autooxidation in solution interferes with the ability of the sulfite ion to enter the cell or, alternatively, significantly lowers the bisulfite concentration so that the cell is not mutagenized. Glutathione mutagenesis appears to occur via a slightly different mechanism. The mutagenicity of glutathione requires metabolism by gamma-glutamyltransferase and is inhibited by free radical scavengers or catalase. This implies that an active oxygen species is the mutagen, and is supported by evidence that 'activated' glutathione does not bind to DNA.

5-(4-Nitrophenyl)-2,4-Pentadien-1-al ("spy dust") and two of its metabolites (4-nitrobenzoic acid (NBA) and 4-nitrohippuric acid) were studied in Salmonella. Both spy dust and NBA were direct acting mutagens and gave slightly enhanced responses in the presence of rat liver S-9. The mutagenicity of "spy dust", but not NBA, was diminished, but not eliminated in Salmonella strains lacking nitroreductase.

The study of electron-withdrawing and electron-donating substituents on the mutagenicity and alkylating ability of phenanthreneimine is continuing. Ring substituents appear to have relatively minor effects on mutagenicity as compared to imine substitutions.

Correlations were made between mutagenicity in Salmonella and carcinogenicity in rodents. A number of factors were examined, including bacterial strain specificity, chemical class, rodent species responsiveness, and tumor location.

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The involvement of free radicals in the mutagenicity of bisulfite, glutathione, and other sulfhydryl-containing chemicals will be further defined. These studies will be extended to a study of the mutagenicity of metals in Salmonella, which also appear to proceed through a free radical or active oxygen involvement. The correlations between Salmonella mutagenesis and mutagenesis in other test systems, and rodent carcinogenicity will be further defined, and specific recommendations will be made regarding the use of the Salmonella assay as a preliminary indicator of carcinogenicity. (CONTACT PERSON: Dr. E. Zeiger)

DNA Repair and Mutagenesis in Drosophila -- Mutation rates are under genetic control. In bacteria and yeast, for example, induced mutation frequencies can be altered by blocking one or another DNA repair pathway. This project is designed to determine the relationship between DNA repair and mutagenesis in Drosophila melanogaster with the general approach being a genetic analysis of mutants that are defective in DNA repair.

One mutator (mu-2) being examined is unable to repair euchromatic X-ray-induced chromosome breaks in the normal way. In its presence broken chromosomes are recovered which do not appear to be capped by a previously existing telomere; that is, terminal deletions are recovered that are not associated with chromosome rearrangements such as translocations. The telomeres of a number of terminally-deleted chromosomes are being cloned in order to characterize them and develop a consensus sequence for functional telomeres in Drosophila. The breakpoints for all of these deletions are within the yellow gene. However, the deletions appear to be slowly enlarging. It may, thus, be impossible to identify the original breakpoint.

A gene controlling DNA repair (mei-41) has been cloned. It has been shown to control the presence of a deoxyribonuclease although it does not code for nuclease.

These studies resulted in four publications in FY 1986 (see references 35 to 38 at the end of the chapter).

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The telomeres on the terminally deleted chromosomes will be cloned. The telomere sequence from a number of these deleted chomosomes will be compared with each other to identify a consensus sequence and compared with the wild type sequence to attempt to identify regions that may be responsible for long-term chromosome stability.

The DNA sequences surrounding mei-41 will be characterized to identify specific controlling regions and elucidate the gene structure. The nature of the mei-41 - nuclease interaction will be pursued by establishing a developmental profile, examining new mei-41 alleles for effects on the nuclease and trying to identify the structural gene for the nuclease. (CONTACT PERSON: Dr. J. Mason)

Xenobiotic Metabolism by Peroxidases -- In addition to the mixed function oxidases, peroxidases also play a role in the metabolism of some xenobiotics and recent evidence implicates peroxidases in the metabolism of benzidine dyes and other procarcinogens to their ultimate carcinogenic form. The metabolic route is different than that observed with mixed function oxidases and often involves one electron oxidation of the xenobiotic and the production of reactive intermediates such as peroxyl radicals. Peroxidases are widely distributed in mammalian tissues and commonly found in epithelial cells that undergo malignant transformation.

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Peroxidases such as prostaglandin H synthase are being coupled to a mammalian cell system so that it can be determined whether metabolites of this enzyme system are mutagenic. Benzidine, amitrole and 2-naphthylamine are compounds that are being examined. The possible mechanisms responsible for the formation of mutagenic metabolites induced by various peroxidases are being investigated. The use of selective inhibitors of the peroxidases are being used to aid in the elucidation of these mechanisms. Studies include the identification of metabolites and effects on DNA induced by this activation system. (CONTACT PERSON: Dr. W. Caspary)

Cell Culture Systems to Study Human and Rodent Differences in Carcinogen Activation -- Species differences in response to chemical carcinogens are known to exist, and understanding the basis of such differences is fundamental to understanding the carcinogenesis process itself and important for extrapolation of rodent carcinogenesis data to the human. Compounds previously tested for genetic toxicity and rodent carcinogenicity by the NTP will be studied for their metabolism and activation to mutagenic products by intact cells from various human and rodent tissues.

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Intact cells from liver, colon and kidney will be prepared from human and rodent tissues by procedures previously developed. Mutagenicity studies will be performed using the cell-mediated *Salmonella typhimurium* or the cell-mediated V79 cell systems depending on the nature of the test chemical. The metabolism of the chemicals by the various cell types from humans and rodents will be analyzed by high pressure liquid chromatography. Chemicals which have demonstrated organ specificity in NTP rodent bioassays have been chosen for study. The results from such studies should allow comparisons of human to rodent tissue activation as well as indicate the degree of interindividual metabolism variation in the human population. (CONTACT PERSON: Dr. R.J. Langenbach)

TABLE 1

CHEMICAL TEST RESULTS FOR MUTAGENICITY IN SALMONELLA ASSAYS IN FY 1986

SEQ. NO.	CHEMICAL	RESULTS * **	CAS NO
1	ACETONE	-	67-64-1
2	ACETYLCHLORIDE	-	75-36-5
3	AF-2	+, +	3688-53-7
4	AFLATOXIN DERIVATIVE (AA34-3-82107)	+	EMTDP-11
5	AFLATOXIN EXTRACT AA 34-10	+	EMTDP-09
6	ALDICARB	-	116-06-3
7	ALDICARB OXIME	-	1646-75-9
8	ALLYL UREA	+	557-11-9
9	2-AMINOBENZIMIDAZOLE	-	934-32-7
10	2-AMINOBENZOTHIAZOLE	-	136-95-8
11	2-AMINO-4-CHLOROBENZOTHIAZOLE	-	19952-47-7
12	2-AMINO-5,6-DIMETHYLBENZOTHIAZOLE	+	29927-08-0
13	2-AMINO-4-METHOXYBENZOTHIAZOLE	+	5464-79-9
14	2-AMINO-4-METHYLBENZOTHIAZOLE	-	1477-42-5
15	2-AMINO-4-(METHYLSULFONYL)PHENOL	-	98-30-6
16	6-AMINO-4-NITRO-1-PHENOL-2-SULFONIC ACID	-	96-67-3
17	2-AMINO-4-PHENYLTHIAZOLE HBR H2O	+	52253-69-7
18	5-AMINO-3-SULFOSALICYLIC ACID	-	6201-87-2
19	2-AMINO-4-THIAZOLEACETIC ACID	?	29676-71-9
20	2-AMINO-4-THIAZOLINE-4-CARBOXYLIC ACID	-	2150-55-2
21	3-AMINOTRIAZOLE	-	61-82-5
22	AMSCO SOLVENT F	-	EMTDP-69
23	AMYL NITRITE	+W, +W	463-04-7
24	ANILAZINE	-	101-05-3
25	O-ANISIDINE	+	90-04-0
26	AROCLOR 1254	-	11097-69-1
27	L-ASCORBIC ACID	-	50-81-7
28	P-AZOXYANISOLE	+	1562-94-3
29	AZOXYMETHANE	+W	25843-45-2
30	BENOMYL	-	17804-35-2
31	BENZIDINE	+	92-87-5
32	BENZOIC ACID	-, -	65-85-0
33	BENZO(E)PYRENE	+	192-97-2
34	BENZOTRICHLORIDE	+	98-07-7
35	BENZOTRIFLUORIDE	-	98-08-8
36	2-BIPHENYLAMINE	+, +, +	90-41-5
37	2-BIPHENYLAMINE HYDROCHLORIDE	+	2185-92-4
38	BIUREA	-	110-21-4
39	BROMOCHLOROMETHANE	+	74-97-5
40	BROMOFORM	?	75-25-2
41	ALPHA-BROMOTOLUENE	+	100-39-0
42	M-BROMOTOLUENE	-	591-17-3

* + = POSITIVE, - = NEGATIVE, ? = EQUIVOCAL, W = WEAK RESPONSE

** RESULTS SEPARATED BY COMMAS REPRESENT MULTIPLE TESTS

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TABLE 1

CHEMICAL TEST RESULTS FOR MUTAGENICITY IN SALMONELLA ASSAYS IN FY 1986

SEQ. NO.	CHEMICAL	RESULTS * **	CAS NO
43	O-BROMOTOLUENE	-	95-46-5
44	P-BROMOTOLUENE	-	106-38-7
45	2-(2-BUTOXYETHOXY)ETHYL THIOCYANATE	-	112-56-1
46	N-BUTYL ACETATE	-	123-86-4
47	BUTYRYL CHLORIDE	+W	141-75-3
48	CAPRYLYL CHLORIDE	+	111-64-8
49	CARBON TETRACHLORIDE	-	56-23-5
50	CARMINIC ACID	+W	1260-17-9
51	N-(3-CHLOROALLYL)HEXAMINIUM CHLORIDE	+W	4080-31-3
52	M-CHLOROBENZOTRIFLUORIDE	-	98-15-7
53	O-CHLOROBENZOTRIFLUORIDE	-	88-16-4
54	CHLORONEB	+	2675-77-6
55	1-CHLORO-1-NITROPROPANE	+	600-25-9
56	2-CHLORO-2-NITRO-PROPANE	+W	594-71-8
57	1-CHLORO-2-PROPANOL	+	127-00-4
58	CHLOROTHIAZIDE	-	58-94-6
59	CHROMIUM CARBONYL	-	13007-92-6
60	C.I. DISPERSE BLUE 27	+	15791-78-3
61	C.I. PIGMENT RED 2	+W	6041-94-7
62	C.I. PIGMENT YELLOW 100	-	12225-21-7
63	COUMAPHOS	-	56-72-4
64	M-CRESIDINE	+	102-50-1
65	CYCLOHEXIMIDE	-	66-81-9
66	N-CYCLOHEXYL-4-METHYLBENZENESULFONAMIDE	-	80-30-8
67	D & C YELLOW NO. 11	+W	8003-22-3
68	DECANE	?	124-18-5
69	DICHLORAN	+	99-30-9
70	DICHLOROACETYL CHLORIDE	+	79-36-7
71	5,6-DICHLORO-2-BENZOTHIAZOLAMINE	.	24072-75-1
72	CIS-1,2-DICHLOROETHYLENE	-	156-59-2
73	5-DIETHYLAMINO-2-NITROSOPHENOL HYDROCHLORIDE	-	25953-06-4
74	2,4-DIMETHOXYANILINE HYDROCHLORIDE	+	54150-69-5
75	N,N-DIMETHYL-P-PHENYLENEDIAMINE	+	99-98-9
76	N,N'-DI-2-NAPTHYL-P-PHENYLENEDIAMINE	+	93-46-9
77	2,4-DINITROPHENOL	-	51-28-5
78	4,4'-DIOCTYLDIPHENYLAMINE	-	101-67-7
79	N,N'-DIPHENYL-P-PHENYLENEDIAMINE	+	74-31-7
80	N,N'-DI-SEC-BUTYL-P-PHENYLDIAMINE	-	101-96-2
81	2,2'-DITHIOBIS-BENZOTHIAZOLE	+	120-78-5
82	EICOSANE	-	112-95-8
83	ELLAGIC ACID	-	476-66-4
84	1,2-EPOXY-3-FLUOROPROPANE	+	503-09-3

* + = POSITIVE, - = NEGATIVE, ? = EQUIVOCAL, W = WEAK RESPONSE
** RESULTS SEPARATED BY COMMAS REPRESENT MULTIPLE TESTS

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TABLE 1

CHEMICAL TEST RESULTS FOR MUTAGENICITY IN SALMONELLA ASSAYS IN FY 1986

SEQ. NO.	CHEMICAL	RESULTS * **	CAS NO.
85	ETHYL ACETATE	-	141-78-6
86	S-(ETHYL)CHLOROTHIOFORMIC ACID	-	2941-64-2
87	S-ETHYL DIPROPYLTHIOCARBAMATE	-	759-94-4
88	ETHYLENEDIAMINE	+W, ?	107-15-3
89	ETHYLENE GLYCOL MONOBUTYL ETHER (EGMBE)	-	111-76-2
90	N-ETHYL-4-METHYLBENZENESULFONAMIDE	-	80-39-7
91	FD & C YELLOW NO. 6	-	2783-94-0
92	GRISEOFULVIN	-	126-07-8
93	4-N-HEXYL-4'-CYANOBIPHENYL	-	41122-70-7
94	8-HYDROXYQUINOLINE SULFATE	+	134-31-6
95	IODOCHLOROHYDROXYQUINOLINE	-	130-26-7
96	IODOFORM	+	75-47-8
97	ISOAMYL ACETATE	-	123-92-2
98	ISOBUTYL ALCOHOL	-	78-83-1
99	ISOPROPANOL	-	67-63-0
100	LUMINOL	-	521-31-3
101	4-METHOXYBENZILIDINE-4'-N-BUTYLANILINE (MBBA)	+	26227-73-6
102	6-METHOXY-2-BENZOTHIAZOLAMINE	+	1747-60-0
103	2-METHOXYETHYL ACETATE	?	110-49-6
104	METHOXYETHYL MERCURY CHLORIDE	-	123-88-6
105	METHYL ACETATE	-	79-20-9
106	4-(6-METHYL-2-BENZOTHIAZOLYL)-BENZENAMINE	+	92-36-4
107	N'-METHYL-N,N-DIPHENYLUREA	-	13114-72-2
108	METHYLETHYL KETONE	-	78-93-3
109	METHYLGLUTARONITRILE	+W	4553-62-2
110	METHYL MERCURIC CHLORIDE	-	115-09-3
111	METHYL MERCURY HYDROXIDE	-	1184-57-2
112	2-METHYL-4-NITROANILINE	+	99-52-5
113	2-METHYL-6-NITROANILINE	+	570-24-1
114	4-METHYL-2-NITROANILINE	+	89-62-3
115	5-METHYL-2-NITROANILINE	-	578-46-1
116	N-METHYL-4-NITROANILINE	+	100-15-2
117	2-METHYL-3-NITRO-BENZOIC ACID	+	1975-50-4
118	3-METHYL-2-NITRO-BENZOIC ACID	+	5437-38-7
119	3-METHYL-4-NITRO-BENZOIC ACID	+	3113-71-1
120	4-METHYL-3-NITRO-BENZOIC ACID	+	96-98-0
121	5-METHYL-2-NITRO-BENZOIC ACID	+	3113-72-2
122	2-METHYL-5-NITROBENZOIC ACID	+	1975-52-6
123	6-METHYLQUINOLINE	+	91-62-3
124	8-METHYLQUINOLINE	+	611-32-5
125	7-METHYLQUINOLINE	+	612-60-2
126	METHYLTIN-TRIS(ISOOCTYLMERCAPTOACETATE)	-	54849-38-6

* + = POSITIVE, - = NEGATIVE, ? = EQUIVOCAL, W = WEAK RESPONSE
** RESULTS SEPARATED BY COMMAS REPRESENT MULTIPLE TESTS

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TABLE 1

CHEMICAL TEST RESULTS FOR MUTAGENICITY IN SALMONELLA ASSAYS IN FY 1986

SEQ. NO.	CHEMICAL	RESULTS * **	CAS NO
127	METRONIDAZOLE	+	443-48-1
128	MICHLER'S KETONE	+	90-94-8
129	MOLYBDENUM TRIOXIDE	-	1313-27-5
130	4-(2-NAPHTHYLAMINO)PHENOL	-	93-45-8
131	NINHYDRIN	?	485-47-2
132	NTA(NITRILOTRIACETIC ACID)	-	139-13-9
133	2-NITRO-1-BUTANOL	-	609-31-4
134	2-NITRODIPHENYLAMINE	-	119-75-5
135	N-NITROSODIPHENYLAMINE	-	86-30-6
136	BETA-NITROSTYRENE	+W	102-96-5
137	5-NITRO-O-TOLUIDINE	+	99-55-8
138	NONYLPHENYL DIPHENYL PHOSPHATE (NPDPP MIXED ISOMERS)	-	64532-97-4
139	2-OCTYL-3-ISOTHIAZOLONE	-	26530-20-1
140	1-PENTANOL	-	71-41-0
141	3-PENTENENITRILE	?	4635-87-4
142	M-PHENETIDINE	+W	621-33-0
143	P-PHENYLENEDIAMINE DIHYDROCHLORIDE	+	624-18-0
144	29H,31H-PHTHALOCYANINE	+	574-93-6
145	PHTHALOCYANINE GREEN	+	1328-53-6
146	PICRYL CHLORIDE	+	88-88-0
147	PROCARBAZINE HYDROCHLORIDE	-	366-70-1
148	1,3-PROPANEDIOL 2-((BENXOYLOXYL)METHYL)-2-METHYL-DIBENZOATE	-	4196-87-6
149	PROPANEDIOL (2,2-BIS (BENZOYLOXY)METHYL)-DIBENZOATE	-	4196-86-5
150	S-(N-PROPYL)CHLOROTHIOFORMIC ACID	+	13889-92-4
151	1,3-PROPYLENE OXIDE	+	503-30-0
152	PYRENE	+	129-00-0
153	RESCINNAMINE	-	24815-24-5
154	SCOPOLAMINE HYDROBROMIDE	-	114-49-8
155	SELENIUM SULFIDE	+	7446-34-6
156	SODIUM CHLORIDE	-	7647-14-5
157	STYRENE	-	100-42-5
158	TETRACHLOROPHTHALIC ACID	+	3682-19-7
159	TETRACHROMIC ACID, POTASSIUM ZINC SALT	+	12433-50-0
160	TETRADECANOIC ACID	-	544-63-8
161	N,N,N',N'-TETRAMETHYL-P-PHENYLENEDIAMINE	+	100-22-1
162	THIOACETAMIDE	-	62-55-5
163	2,2'-THIOBIS(4,6-DICHLOROPHENOL)	?	97-18-7
164	THIOPHANATE M	?	23564-05-8
165	O-TOLUALDEHYDE	-	529-20-4
166	M-TOLUIDINE HYDROCHLORIDE	-	638-03-9
167	1,1,2-TRICHLOROETHANE	-	79-00-5
168	2,3,4-TRICHLORONITROBENZENE	+	17700-09-3

* + = POSITIVE, - = NEGATIVE, ? = EQUIVOCAL, W = WEAK RESPONSE
** RESULTS SEPARATED BY COMMAS REPRESENT MULTIPLE TESTS

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TABLE 1

CHEMICAL TEST RESULTS FOR MUTAGENICITY IN SALMONELLA ASSAYS IN FY 1986

SEQ. NO.	CHEMICAL	RESULTS * **	CAS NO.
169	2, 4, 5-TRICHLORONITROBENZENE	+	89-69-0
170	2, 3, 4-TRICHLOROPHENOL	-	15950-66-0
171	2, 3, 5-TRICHLOROPHENOL	-	933-78-8
172	2, 3, 6-TRICHLOROPHENOL	-	933-75-5
173	3, 4, 5-TRICHLOROPHENOL	-	609-19-8
174	1, 3, 5-TRIGLYCIDYL ISOCYANURATE	+	2451-62-9
175	TRIPHENYLAMINE	-	603-34-9
176	TRIPHENYLTIN HYDROXIDE	-	76-87-9
177	TRIS(2-CHLOROISOPROPYL)PHOSPHATE	-	13674-84-5
178	TRIS(1, 3-DICHLORO-2-PROPYL) PHOSPHATE	+, +	13674-87-8
179	1, 3, 5-TRIS(2-HYDROXYETHYL)TRIAZINE-2, 4, 6-TRIONE	-	839-90-7
180	L-TRYPTOPHAN	-	73-22-3
181	WATER	+W	7732-18-5
182	2, 6-XYLIDINE	+W, +W	87-62-7

* + = POSITIVE, - = NEGATIVE, ? = EQUIVOCAL, W = WEAK RESPONSE
** RESULTS SEPARATED BY COMMAS REPRESENT MULTIPLE TESTS

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TABLE 2

CHEMICALS SELECTED FOR MUTAGENICITY TESTING IN SALMONELLA IN FY 1987

SEQ. NO.	CHEMICAL	CAS NO.
1	ACENAPHTHENE	83-32-9
2	ACETIC ACID	64-19-7
3	ACETOHEXAMIDE	968-81-0
4	2-ACETYLAMINO-4-METHYLPHENOL	6375-17-3
5	4-ACETYL PYRIDINE	1122-54-9
6	ALDRIN	309-00-2
7	AMILORIDE HYDROCHLORIDE	2016-88-8
8	2-(4-AMINOPHENYL)-6-METHYL-7-BENZOTHIAZOLE SULFONIC ACID	130-17-6
9	AMPHOTERICIN B	1397-89-3
10	AMSCO SOLVENT F (100%)	AMSCO100SOLF
11	ANTIMONY POTASSIUM TARTRATE	28300-74-5
12	5-AZACYTIDINE	320-67-2
13	AZATHIOPRINE	446-86-6
14	BARIUM CHLORIDE DIHYDRATE	10326-27-9
15	BENZO(B)FLUORANTHENE	205-99-2
16	BENZO(K)FLUORANTHENE	207-08-9
17	BENZOYL CHLORIDE	98-88-4
18	BENZYL SULFIDE	538-74-9
19	BERYLLIUM SULFATE TETRAHYDRATE	7787-56-6
20	(4,4'-BITHIAZOLE)-2,2'-DIAMINE	58139-59-6
21	BETA-BROMO-BETA-NITROSTYRENE	7166-19-0
22	BROMOPICRIN	464-10-8
23	1,3-BUTADIENE	106-99-0
24	N-BUTANE	106-97-8
25	4-BUTOXYBENZYL-4-ETHYLANILINE	29743-15-5
26	DI-N-BUTYL ETHER	142-96-1
27	T-BUTYLHYDROQUINONE	1948-33-0
28	BUTYRIC ACID	107-92-6
29	CAPTAN	133-06-2
30	CARBARSONE	121-59-5
31	4-(CHLOROACETYL)ACETANILIDE	140-49-8
32	2-CHLOROBENZALDEHYDE	89-98-5
33	4-CHLOROBENZALDEHYDE	104-88-1
34	M-CHLOROBENZOIC ACID	535-80-8
35	O-CHLOROBENZOIC ACID	118-91-2
36	P-CHLOROBENZOIC ACID	74-11-3
37	4-CHLORO-M-CRESOL	59-50-7
38	4-CHLORO-O-CRESOL	1570-64-5
39	1-CHLORONAPHTHALENE	90-13-1
40	2-CHLORONAPHTHALENE	91-58-7
41	CHLOROTHIOFORMIC ACID	2812-73-9
42	P-CHLOROTOLUENE	106-43-4
43	C.I. DIRECT BLACK 114	61703-05-7
44	C.I DIRECT ORANGE 6	6637-88-3
45	C.I PIGMENT RED 81	12224-98-5
46	CLONITRALID	1420-04-8

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TABLE 2

CHEMICALS SELECTED FOR MUTAGENICITY TESTING IN SALMONELLA IN FY 1987

SEQ. NO.	CHEMICAL	CAS NO.
47	COBALT SULFATE HEPTAHYDRATE	10026-24-1
48	CREOSOTE	8021-39-4
49	P-CUMYL PHENYL GLYCIDYL ETHER	61578-04-9
50	CYCLOPENTAPHENANTHRENE	203-64-5
51	CYCLOSPORIN A	59865-13-3
52	DDD	6088-51-3
53	2,4-DIAMINODIPHENYLMETHANE	1206-52-2
54	1,2-DIBROMOETHANE (ETHYLENE DIBROMIDE)	106-93-4
55	2,4-DICHLOROANILINE	554-00-7
56	2,4-DICHLOROBENZALDEHYDE	874-42-0
57	2,6-DICHLOROBENZALDEHYDE	83-38-5
58	3,4-DICHLOROBENZALDEHYDE	6287-38-3
59	DICHLOROBENZOIC ACID	35915-19-6
60	2,2'-DICHLOROBIPHENYL	13029-08-8
61	CIS-DICHLORODIAMINE PLATINUM	15663-27-1
62	DICHLORODIPHENYLTRICHLOROETHANE	50-29-3
63	1,1-DICHLOROETHANE	75-34-3
64	DICHLOROMETHANE (METHYLENE CHLORIDE)	75-09-2
65	ALPHA,ALPHA-DICHLOROTOLUENE	611-19-8
66	DIETHYLDICHLOROSILANE	1719-53-5
67	DIETHYLENE GLYCOL MONOBUTYL ETHER	112-34-5
68	N,N-DIETHYL-4-((5-NITRO-2-THIAZOLYL)AZO) BENZENAMINE	54289-46-2
69	DIGITONIN	11024-24-1
70	2,2-DIMETHYLBUTANE	75-83-2
71	2,3-DIMETHYLBUTANE	79-29-8
72	DIMETHYL DITALLOW AMMONIUM CHLORIDE	68783-78-8
73	2,5-DIMETHYLFURAN	625-86-5
74	DIMETHYLNAPHTHALENE	28804-88-8
75	1,6-DIMETHYLNAPHTHALENE	575-43-9
76	N,N-DIMETHYL-N-OCTADECYLBENZENEMETHANAMINIUM CHLORIDE	122-19-0
77	2,3-DIMETHYL-1-PENTANOL	10143-23-4
78	DIMETHYL PHENOL	1300-71-6
79	DIMETHYLSUCCINATE	106-65-0
80	DIMETHYL SULFOXIDE	67-68-5
81	DINITROPYRENE MIXTURE	EMTDP-35
82	TERT-DODECYL MERCAPTAN	25103-58-6
83	ECONAZOLE	24169-02-6
84	2,3-EPOXYBUTANE	3266-23-7
85	2,3-EPOXY-2,3-DIMETHYLBUTANE	5076-20-0
86	1,2-EPOXY-1,1,2,3,3,3-HEXAFLUOROPROPANE	428-59-1
87	ETHYL ALCOHOL	64-17-5
88	ETHYL CHLORIDE	75-00-3
89	N-ETHYL-N,N-DIPHENYLUREA	18168-01-9
90	ETHYLENE GLYCOL MONOMETHYL ETHER (EGMME)	109-86-4
91	ETHYLENE OXIDE	75-21-8
92	ETHYL ETHER	60-29-7

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TABLE 2

CHEMICALS SELECTED FOR MUTAGENICITY TESTING IN SALMONELLA IN FY 1987

SEQ. NO.	CHEMICAL	CAS NO.
93	N-ETHYL-4-NITROANILINE	3665-80-3
94	O-ETHYL PHENOL	90-00-6
95	FLURAZEPAM	17617-23-1
96	FORMIC ACID	64-18-6
97	FUMARIC ACID DINITRILE	EMTDP-73
98	GALLIUM ARSENIDE	1303-00-0
99	GILSONITE	12002-43-6
100	GUAR GUM	9000-30-0
101	GUM ARABIC	9000-01-5
102	N-HEPTANAL	111-71-7
103	N-HEPTANOIC ACID	111-14-8
104	1,2,3,4,7,7-HEXACHLOROBICYCLO(2.2.1)HEPTA-2,5-DIENE	3389-71-7
105	1,2,3,6,7,8-HEXACHLORODIBENZO-P-DIOXIN	57653-85-7
106	1,2,3,7,8,9-HEXACHLORODIBENZO-P-DIOXIN	19408-74-3
107	1,1,1,3,3,3-HEXAFLUORO-2-PROPANOL	920-66-1
108	HEXYLBENZOATE	6789-88-4
109	HYCANTHONE METHANESULFONATE	23255-93-8
110	HYDROXYLAMINE HYDROCHLORIDE	5470-11-1
111	ISOPENTANE	78-78-4
112	ISOPROPYL ACETATE	108-21-4
113	LANTHANUM NITRATE HEXAHYDRATE	10277-43-7
114	LAURYL CHLORIDE	112-52-7
115	LOCUST BEAN GUM	9000-40-2
116	MELPHALAN	148-82-3
117	2-MERCAPTO-4-METHYL-5-THIAZOLYL METHYL KETONE	7725-93-1
118	6-MERCAPTOPURINE MONOHYDRATE	6112-76-1
119	METHANE	74-82-8
120	3-((METHOXYCARBONYL)AMINO)PHENYL N-(3-METHYLPHENYL)CARBAMATE	13684-63-4
121	METHOXYFLURANE	76-38-0
122	8-METHOXYPSORALEN	298-81-7
123	METHYLBENZOATE	93-58-3
124	P-METHYL BENZYL ALCOHOL	589-18-4
125	METHYL BIPHENYL	28652-72-4
126	METHYL CHLORIDE	74-87-3
127	METHYLCYCLOPENTANE	96-37-7
128	2,2'-METHYLENE-BIS (4-CHLOROPHENOL)	97-23-4
129	2,2'-METHYLENE BIS(PHENYLENEOXYMETHYLENE)BISOXIRANE	39817-09-9
130	METHYLENE BIS(THIOCYANATE)	6317-18-6
131	2-METHYL-2-ETHOXYPROPANE	637-92-3
132	METHYL ETHYL KETOXIME	96-29-7
133	9-METHYL FLUORENE	2523-37-7
134	METHYL FORMATE	107-31-3
135	METHYL-P-FORMYL BENZOATE	1571-08-0
136	2-METHYL FURAN	534-22-5
137	2-METHYLGLYCIDYL ACRYLATE	19900-46-0
138	METHYL ISOBUTYL KETONE	108-10-1

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TABLE 2

CHEMICALS SELECTED FOR MUTAGENICITY TESTING IN SALMONELLA IN FY 1987

SEQ. NO.	CHEMICAL	CAS NO.
139	3-METHYL-6-METHOXY-2-AMINO-BENZOTHIAZOLIUM CHLORIDE	NOCAS0884
140	METHYL NAPHTHALENE	1321-94-4
141	METHYL PENTACHLOROSTEARATE	26638-28-8
142	1-METHYL PHENANTHRENE	832-69-9
143	2-METHYL PHENANTHRENE	2531-84-2
144	1-METHYL PYRENE	2381-21-7
145	ALPHA-METHYLSTYRENE	98-83-9
146	METHYL SUCCINIC ACID	498-21-5
147	METHYL-P-TOLUATE	99-75-2
148	METHYLTRIFLUOROMETHANESULFONATE	333-27-7
149	METHYL VINYL KETONE	78-94-4
150	MONOSODIUM GLUTAMATE	142-47-2
151	NICKEL SUBSULFIDE	12035-72-2
152	NIFEDIPINE	21829-25-4
153	1-NITROPYRENE	5522-43-0
154	N-NITROSO-N-ETHYLURETHANE	614-95-9
155	NONANE	111-84-2
156	OLIVETOL	500-66-3
157	OXAZEPAM	604-75-1
158	1,1-OXYBIS METHYLENE, BIS BENZENE	103-50-4
159	A,A,A,3,4-PENTACHLOROTOLUENE	13014-24-9
160	2,4,A,A,A-PENTACHLOROTOLUENE	13014-18-1
161	N-PENTANAL	110-62-3
162	N-PENTANE	109-66-0
163	2-PENTANONE	107-87-9
164	PERCHLOROMETHYL MERCAPTAN	594-42-3
165	PHENYLPHOSPHINE	638-21-1
166	PHOSPHATE ESTER MIXTURE:NC220	EMTDP-45
167	PHTHALIC ACID	88-99-3
168	POLYETHYLENE AS	9002-88-4
169	POLYSTYRENE	9003-53-6
170	POLYTHIAZIDE	346-18-9
171	POTASSIUM DICHROMATE	7778-50-9
172	PROPIONIC ACID	79-09-4
173	PROPYLENE	115-07-1
174	QUERCETIN	117-39-5
175	GUINETHAZONE (AQUAMOX)	73-49-4
176	SELSUN	SELSUN
177	SODIUM CYANURATE	2624-17-1
178	SPIRO(ISOBENZOFURAN-1 (3H) 9'-(9H)XANTHEN)-3-ONE 2',4',4',7'-TETRABROMO-3',6'-DIHYDROXY, DISODIUM SALT	17372-87-1
179	TARA GUM	39300-88-4
180	1,2,3,4-TCDD	30746-58-8
181	1,1,2,3-TETRACHLORO-BUTADIENE	921-09-5
182	2,3,5,6-TETRACHLORO-4-NITROANISOLE	2438-88-2
183	TETRACHLOROPHTHALIC ANHYDRIDE	117-08-8
184	TETRAFLUOROETHYLENE	116-14-3

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TABLE 2

CHEMICALS SELECTED FOR MUTAGENICITY TESTING IN SALMONELLA IN FY 1987

SEQ. NO.	CHEMICAL	CAS NO.
185	TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM SULFATE	55566-30-8
186	1,3,6,8-TETRANITROPYRENE	28767-61-5
187	P-TOLUIC ACID	25567-10-6
188	TRIBENZYL ISOCYANURATE	606-03-1
189	TRIBUTYL PHOSPHATE	126-73-8
190	2,4,6-TRICHLOROANILINE	634-93-5
191	TRICHLOROMELAMINE	7673-09-8
192	2,4,6-TRICHLORONITROBENZENE	18708-70-8
193	3,4,6-TRICHLORO-2-NITROPHENOL	82-62-2
194	TRIMETHYL ISOCYANURATE	827-16-7
195	TRIMETHYLPHOSPHATE	512-56-1
196	1,3,6-TRINITROPYRENE	75321-19-6
197	2,4,6-TRINITROTOLUENE	118-96-7
198	TRI-N-PROPYLAMINE	102-69-2
199	TRIS(CARBAMOYLMETHYL)ISOCYANURATE	1843-48-7
200	TRIS(2-KETOPROPYL)ISOCYANURATE	61050-97-3
201	TRISODIUM NITRILOTRIACETATE MONOHYDRATE	18662-53-8
202	TRIS(TRIPHENYLSTANNYL)ISOCYANURATE	752-74-9
203	URETHANE	51-79-6
204	VALIUM	439-14-5
205	VANADIUM PENTOXIDE	1314-62-1
206	VINYLIDENE FLUORIDE	75-38-7

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TABLE 3

CHEMICAL TEST RESULTS FOR HERITABLE GENETIC EFFECTS IN DROSOPHILA IN FY 1986

SEQ. NO.	CHEMICAL	RESULTS *		CAS NO.
		SLRL	** RT	
1	ACRYLONITRILE	+	-	107-13-1
2	9-AMINOACRIDINE, MONOHYDROCHLORIDE, MONOHYDRATE	-	ND	52417-22-8
3	BENZO(A)PYRENE	-	ND	50-32-8
4	BIS(2-CHLOROETHYL)ETHER	+	-	111-44-4
5	GAMMA-BUTYROLACTONE	-	ND	96-48-0
6	2-CHLOROMETHYLPYRIDINE HYDROCHLORIDE	+	-	6959-47-3
7	1-CHLORO-2-PROPANOL	+	-	127-00-4
8	C. I BASIC ORANGE 2	-	ND	532-82-1
9	COUMARIN	-	ND	91-64-5
10	CYTEMBENA	?	ND	21739-91-3
11	DIMETHYLETHANOLAMINE	-	ND	108-01-0
12	DIMETHYLFORMAMIDE	?	ND	68-12-2
13	DIMETHYLOLDIHYDROXYETHYLENEUREA	+	-	1854-26-8
14	DIMETHYLVINYL CHLORIDE (DMVC)	+	+	513-37-1
15	ETHYLENE THIOUREA	+	-	96-45-7
16	EUGENOL	-	ND	97-53-0
17	FURAN	-	ND	110-00-9
18	HC BLUE 1	-	ND	2784-94-3
19	HC BLUE 2	?	ND	33229-34-4
20	HEXACHLOROCYCLOPENTADIENE	-	ND	77-47-4
21	HEXAMETHYL-P-ROSANILINE CHLORIDE	-	ND	548-62-9
22	8-HYDROXYQUINOLINE SULFATE	?	ND	134-31-6
23	ISATIN-5-SULFONIC ACID SODIUM SALT	+	-	80789-74-8
24	ISOAMYL ACETATE	-	ND	123-92-2
25	MERCURIC CHLORIDE	-	ND	7487-94-7
26	3-METHYLCHOLANTHRENE	-, -	ND, ND	56-49-5
27	M-NITROPHENOL	?	ND	554-84-7
28	PHENAZOPYRIDINE HYDROCHLORIDE	-	ND	136-40-3
29	PYRIDINE	+, -	-, ND	110-86-1
30	QUINOLINE	-	ND	91-22-5
31	ROXARSONE	?	ND	121-19-7
32	TRICHLOROETHYLENE (WITHOUT EPICHLOROHYDRIN)	?	ND	79-01-6
33	VINYLIDENE CHLORIDE	-	ND	75-35-4

* + = POSITIVE, - = NEGATIVE, ? = EQUIVOCAL, W = WEAK RESPONSE

** RESULTS SEPARATED BY COMMAS REPRESENT MULTIPLE TESTS

SLRL = SEX-LINKED RECESSIVE LETHAL, RT = RECIPROCAL TRANSLOCATION

ND = NOT DONE

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TABLE 4

CHEMICALS SELECTED TO BE TESTED FOR HERITABLE GENETIC EFFECTS IN DROSOPHILA IN FY 1987

SEQ. NO.	CHEMICAL	CAS NO.
1	ACRYLAMIDE	79-06-1
2	AMPHETAMINE SULFATE	60-13-9
3	L-ASCORBIC ACID	50-81-7
4	BENZENE	71-43-2
5	BENZIDINE	92-87-5
6	BENZOIN	119-53-9
7	BISPHENOL A	80-05-7
8	1,3-BUTADIENE	106-99-0
9	N-BUTANE	106-97-8
10	N-BUTYL ACRYLATE	141-32-2
11	CAPROLACTAM	105-60-2
12	CARBON TETRACHLORIDE	56-23-5
13	3-CHLORO-2-METHYLPROPENE	563-47-3
14	4-CHLORO-M-PHENYLENEDIAMINE	5131-60-2
15	4-CHLORO-O-PHENYLENEDIAMINE	95-83-0
16	2-CHLORO-P-PHENYLENEDIAMINE SULFATE	61702-44-1
17	CHLOROPRENE	126-99-8
18	3-CHLORO-P-TOLUIDINE	95-74-9
19	4-CHLORO-O-TOLUIDINE HYDROCHLORIDE	3165-93-3
20	C. I. ACID ORANGE 10	1936-15-8
21	C. I ACID RED 14	3567-69-9
22	C. I. DISPERSE YELLOW 3	2832-40-8
23	C. I. SOLVENT YELLOW 14	842-07-9
24	2,4-DIAMINOTOLUENE	95-80-7
25	1,2-DIBROMOETHANE (ETHYLENE DIBROMIDE)	106-93-4
26	DIBROMOMANNITOL	488-41-5
27	1,2-DICHLOROBENZENE (O-DICHLOROBENZENE)	95-50-1
28	CIS-DICHLORODIAMINE PLATINUM	15663-27-1
29	2,6-DICHLORO-P-PHENYLENEDIAMINE	609-20-1
30	EPICHLORHYDRIN	106-89-8
31	ETHOXYLATED DODECYL ALCOHOL	9002-92-0
32	ETHYL ALCOHOL	64-17-5
33	ETHYLENE OXIDE	75-21-8
34	FD & C YELLOW NO. 6	2783-94-0
35	FORMAMIDE	75-12-7
36	GERANYL ACETATE	105-87-3
37	HEXAMETHYL PHOSPHORAMIDE	680-31-9
38	2-HYDROXY-1,4-NAPHTHOQUINONE	83-72-7
39	8-HYDROXYQUINOLINE	148-24-3
40	ISOPENTANE	78-78-4
41	MALAOXON	1634-78-2
42	D-MANNITOL	69-65-8
43	DL-MENTHOL	15356-70-4
44	6-MERCAPTOPURINE MONOHYDRATE	6112-76-1
45	4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE	13552-44-8
46	MYLERAN	55-98-1

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TABLE 4

CHEMICALS SELECTED TO BE TESTED FOR HERITABLE GENETIC EFFECTS IN DROSOPHILA IN FY 1987

SEQ. NO.	CHEMICAL	CAS NO.
47	O-NITROPHENOL	88-75-5
48	4-NITRO-O-PHENYLENEDIAMINE	99-56-9
49	4,4'-OXYDIANILINE	101-80-4
50	P-PHENYLENEDIAMINE DIHYDROCHLORIDE	624-18-0
51	PROPYLENE	115-07-1
52	1,2-PROPYLENE OXIDE	75-56-9
53	PROPYL GALLATE	121-79-9
54	QUINOLINE SULFATE	530-66-5
55	SELENIUM SULFIDE	7446-34-6
56	STANNOUS CHLORIDE	7772-99-8
57	SULFISOXAZOLE	127-69-5
58	TETRACHLOROPHTHALIC ANHYDRIDE	117-08-8
59	1-TRANS-DELTA-9-TETRAHYDROCANNABINOL	1972-08-3
60	3,3',5,5'-TETRAMETHYLBENZIDINE	54827-17-7
61	TITANIUM DIOXIDE	13463-67-7
62	2,6-TOLUENEDIAMINE DIHYDROCHLORIDE	15481-70-6
63	1,1,2-TRICHLOROETHANE	79-00-5
64	URETHANE	51-79-6

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TABLE 5

CHEMICAL TEST RESULTS FOR MUTAGENICITY IN L5178Y MOUSE LYMPHOMA CELLS IN FY 1986

SEQ. NO.	CHEMICAL	RESULTS *	CAS NO
1	ALLYL ISOVALERATE	+	2835-39-4
2	11-AMINOUNDECANOIC ACID	-	2432-99-7
3	L-ASCORBIC ACID	+	50-81-7
4	5-AZACYTIDINE	+	320-67-2
5	2-BIPHENYLAMINE HYDROCHLORIDE	+	2185-92-4
6	BISPHENOL A	-	80-05-7
7	CHLOROBENZENE	+	108-90-7
8	CHLORODIBROMOMETHANE	+	124-48-1
9	CHLORPHENIRAMINE MALEATE	-	113-92-8
10	CHLORPROPAMIDE	-	94-20-2
11	C.I. ACID RED 14	-	3567-69-9
12	C.I. ACID YELLOW 73 (FLUORESCEIN SODIUM)	+	518-47-8
13	C.I. DISPERSE YELLOW 3	+	2832-40-8
14	C.I. SOLVENT YELLOW 14	+	842-07-9
15	CYTARABINE HYDROCHLORIDE	+	69-74-9
16	CYTEMBENA	+	21739-91-3
17	D & C RED NO. 9	-	5160-02-1
18	1,2-DIBROMO-3-CHLOROPROPANE	+	96-12-8
19	1,2-DIBROMO-4-(1,2-DIBROMOETHYL)CYCLOHEXANE	+	3322-93-8
20	1,2-DICHLOROPROPANE (PROPYLENE DICHLORIDE)	+	78-87-5
21	1,3-DICHLOROPROPENE (TELONE II)	+	542-75-6
22	DIELDRIN	+	60-57-1
23	DI(2-ETHYLHEXYL)ADIPATE	-	103-23-1
24	2,6-DIISOCYANATOTOLUENE	+	91-08-7
25	DIMETHYL TEREPHTHALATE	-	120-61-6
26	ENDOSULFAN	+	115-29-7
27	ENDRIN	-	72-20-8
28	EPHEDRINE SULFATE	-	134-72-5
29	ETHOXYLATED DODECYL ALCOHOL	-	9002-92-0
30	ETHYL ACRYLATE	+	140-88-5
31	ETHYLBENZENE	+	100-41-4
32	ETHYLENEDIAMINE TETRAACETIC ACID (EDTA)	-	150-38-9
33	ETHYLENE THIOUREA	+	96-45-7
34	EUGENOL	+	97-53-0
35	FD & C YELLOW NO. 6	+	2783-94-0
36	IRON DEXTRAN	-	9004-66-4
37	D-LIMONENE	-	5989-27-5
38	LITHOCHOLIC ACID	+	434-13-9
39	MALAOXON	+	1634-78-2
40	D-MANNITOL	-	69-65-8
41	DL-MENTHOL	-	15356-70-4
42	METHAPYRILENE HYDROCHLORIDE	-	135-23-9

* + = POSITIVE, - = NEGATIVE, ? = EQUIVOCAL, W = WEAK RESPONSE

** RESULTS SEPARATED BY COMMAS REPRESENT MULTIPLE TESTS

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TABLE 5

CHEMICAL TEST RESULTS FOR MUTAGENICITY IN L5178Y MOUSE LYMPHOMA CELLS IN FY 1986

SEQ. NO.	CHEMICAL	RESULTS *	CAS NO
43	N-METHYLCARBAMIC ACID, ETHYL ESTER	+	105-40-8
44	4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE	+	13552-44-8
45	MONURON	?	150-68-5
46	NITROFEN	+	1836-75-5
47	4,4'-OXYDIANILINE	+	101-80-4
48	PHENAZOPYRIDINE HYDROCHLORIDE	+	136-40-3
49	PHENOL	+	108-95-2
50	1-PHENYL-3-METHYL-5-PYRAZOLONE	+	89-25-8
51	PHTHALAMIDE	−	88-96-0
52	POLYBROMINATED BIPHENYL MIXTURE (FIREMASTER FF-1)	−	67774-32-7
53	POTASSIUM CHLORIDE	−	7447-40-7
54	PROPYL GALLATE	+	121-79-9
55	RESERPINE	−	50-55-5
56	SELENIUM SULFIDE	+	7446-34-6
57	SODIUM DIETHYLDITHIOCARBAMATE	+	148-18-5
58	SODIUM (2-ETHYLHEXYL)ALCOHOL SULFATE	−	126-92-1
59	SODIUM XYLENESULFONATE	?	1300-72-7
60	STANNOUS CHLORIDE	−	7772-99-8
61	SUCCINIC ACID 2,2-DIMETHYLHYDRAZIDE	?	1596-84-5
62	SULFISOXAZOLE	+	127-69-5
63	4,4'-SULFONYLDIANILINE	−	80-08-0
64	2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN	−	1746-01-6
65	1,1,1,2-TETRACHLOROETHANE	−, +	630-20-6
66	TETRACHLOROETHYLENE	+	127-18-4
67	TETRAETHYLTHIURAM DISULFIDE	+	97-77-8
68	TITANIUM DIOXIDE	−	13463-67-7
69	2,6-TOLUENEDIAMINE DIHYDROCHLORIDE	+	15481-70-6
70	2,4-TOLUENE DIISOCYANATE	+	584-84-9
71	2,4,6-TRICHLOROPHENOL	+	88-06-2
72	TRIS(2-ETHYLHEXYL)PHOSPHATE	−	78-42-2
73	4-VINYLCYCLOHEXENE	+	100-40-3
74	ZEARALENONE	−	17924-92-4
75	ZIRAM	+	137-30-4

* + = POSITIVE, − = NEGATIVE, ? = EQUIVOCAL, W = WEAK RESPONSE
** RESULTS SEPARATED BY COMMAS REPRESENT MULTIPLE TESTS

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TABLE 6

CHEMICALS SELECTED TO BE TESTED FOR MUTAGENICITY IN L5178Y MOUSE LYMPHOMA CELLS IN FY 1987

SEQ. NO.	CHEMICAL	CAS NO
1	ACETAMINOPHEN	103-90-2
2	ACETIC ACID	64-19-7
3	ACETOHEXAMIDE	968-81-0
4	4-ACETYLAMINOFLUORENE	28322-02-3
5	ALLYL GLYCIDYL ETHER	106-92-3
6	ALLYL UREA	557-11-9
7	1-AMINO-2,4-DIBROMOANTHRAQUINONE	81-49-2
8	3-AMINOTRIAZOLE	61-82-5
9	AMPHETAMINE SULFATE	60-13-9
10	P-ANISIDINE HYDROCHLORIDE	20265-97-8
11	5-AZA-2'-DEOXYCYTIDINE	2353-33-5
12	O-BENZYL-P-CHLOROPHENOL	120-32-1
13	BROMOBENZENE	108-86-1
14	1,3-BUTADIENE	106-99-0
15	2-(2-BUTOXYETHOXY)ETHYL THIOCYANATE	112-56-1
16	BUTYRIC ACID	107-92-6
17	N-BUTYRIC ACID, METHYL ESTER	623-42-7
18	GAMMA-BUTYROLACTONE	96-48-0
19	CALCIUM CHROMATE	13765-19-0
20	CALCIUM CYANAMIDE	156-62-7
21	CAPROIC ACID	142-62-1
22	CARBROMAL	77-65-6
23	D-CARVONE	2244-16-8
24	CHLORDECONE (KEPONE)	143-50-0
25	CHLOROACETOPHENONE (CN)	532-27-4
26	4-(CHLOROACETYL)ACETANILIDE	140-49-8
27	P-CHLOROANILINE	106-47-8
28	M-CHLOROANILINE	108-42-9
29	O-CHLOROANILINE	95-51-2
30	2-CHLOROETHYLTRIMETHYLAMMONIUM CHLORIDE	999-81-5
31	2-CHLOROMETHYLPYRIDINE HYDROCHLORIDE	6959-47-3
32	3-CHLOROMETHYLPYRIDINE HYDROCHLORIDE	6959-48-4
33	2-CHLORO-P-PHENYLENEDIAMINE SULFATE	61702-44-1
34	3-CHLORO-P-TOLUIDINE	95-74-9
35	C.I. ACID ORANGE 10	1936-15-8
36	C.I. ACID ORANGE 3	6373-74-6
37	C.I. ACID RED 114	6459-94-5
38	C.I. DIRECT BLUE 218	28407-37-6
39	C.I. DIRECT BLUE 15	2429-74-5
40	C.I. PIGMENT RED 3	2425-85-6
41	C.I. VAT YELLOW 4	128-66-5
42	TRANS-CINNAMALDEHYDE	14371-10-9
43	CITRIC ACID	77-92-9
44	COCONUT DIETHANOLAMIDE	68603-42-9
45	COUMAPHOS	56-72-4
46	COUMARIN	91-64-5

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TABLE 6

CHEMICALS SELECTED TO BE TESTED FOR MUTAGENICITY IN L5178Y MOUSE LYMPHOMA CELLS IN FY 1987

SEQ. NO.	CHEMICAL	CAS NO.
47	CROTONALDEHYDE	4170-30-3
48	4,4'-DIAMINO-2,2'-STILBENEDISULFONIC ACID	81-11-8
49	DIARYLANILIDE YELLOW	6358-85-6
50	DIBENZO-P-DIOXIN	262-12-4
51	DIBUTYL PHTHALATE	84-74-2
52	5,6-DICHLORO-2-BENZOTHIAZOLAMINE	24072-75-1
53	1,3-DICHLORO-5,5-DIMETHYLHYDANTOIN	118-52-5
54	TRANS-1,2-DICHLOROETHYLENE	156-60-5
55	CIS-1,2-DICHLOROETHYLENE	156-59-2
56	N,N'-DICYCLOHEXYLTHIOUREA	1212-29-9
57	DIETHYL PHTHALATE	84-66-2
58	3,4-DIHYDROCOUMARIN	119-84-6
59	DIMETHOATE	60-51-5
60	DIMETHYL PHTHALATE	131-11-3
61	N,N-DIMETHYLUREA	96-31-1
62	2,4-DINITROANILINE	97-02-9
63	2,4-DINITROTOLUENE	121-14-2
64	DIOXATHION	78-34-2
65	DIPHENHYDRAMINE HYDROCHLORIDE	147-24-0
66	DIPHENYLHYDANTOIN (PHENYTOIN)	57-41-0
67	DOXYLAMINE SUCCINATE	562-10-7
68	EPINEPHRINE	51-43-4
69	1,2-EPOXYBUTANE	106-88-7
70	ETHIONAMIDE	536-33-4
71	ETHYL BROMIDE	74-96-4
72	MONO(2-ETHYLHEXYL)ADIPATE	4337-65-9
73	FORMULATED FENAMINOSULF	140-56-7
74	5-FLUORO-2'-DEOXYCYTIDINE	10356-76-0
75	FORMIC ACID	64-18-6
76	GLUTARIC ACID	110-94-1
77	HC YELLOW 4	52551-67-4
78	HEPTACHLOR	76-44-8
79	HEXACHLORO-1,3-BUTADIENE	87-68-3
80	HEXACHLOROCYCLOPENTADIENE	77-47-4
81	HEXACHLOROETHANE	67-72-1
82	N-HEXANE	110-54-3
83	IODOFORM	75-47-8
84	LAURIC ACID DIETHANOLAMINE CONDENSATE	120-40-1
85	LEAD DIMETHYLDITHIOCARBAMATE	19010-66-3
86	LINDANE	58-89-9
87	MALATHION	121-75-5
88	MALONIC ACID	141-82-2
89	MANGANESE SULFATE MONOHYDRATE	10034-96-5
90	2-MERCAPTOBENZIMIDAZOLE	583-39-1
91	MERCAPTOBENZOTHIAZOLE	149-30-4
92	6-METHOXY-2-BENZOTHIAZOLAMINE	1747-60-0

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TABLE 6

CHEMICALS SELECTED TO BE TESTED FOR MUTAGENICITY IN L5178Y MOUSE LYMPHOMA CELLS IN FY 1987

SEQ. NO.	CHEMICAL	CAS NO.
93	8-METHOXYPSORALEN	298-81-7
94	METHYL ACETATE	79-20-9
95	4-(6-METHYL-2-BENZOTHIAZOLYL)-BENZENAMINE	92-36-4
96	METHYL CAPROATE	106-70-7
97	METHYL CARBAMATE	598-55-0
98	METHYLDOPA	555-30-6
99	METHYL FORMATE	107-31-3
100	N-METHYLOLACRYLAMIDE	924-42-5
101	METHYL PARATHION	298-00-0
102	METHYL STEARATE	112-61-8
103	METHYL VALERATE	624-24-8
104	MOLYBDENUM TRIOXIDE	1313-27-5
105	MONO(2-ETHYLHEXYL)PHTHALATE	4376-20-9
106	N-(1-NAPHTHYL)ETHYLENEDIAMINE DIHYDROCHLORIDE	1465-25-4
107	4-NITROANTHRANILIC ACID	619-17-0
108	P-NITROPHENOL	100-02-7
109	N-NITROSODIETHANOLAMINE	1116-54-7
110	P-NITROTOLUENE	99-99-0
111	OLEIC ACID DIETHANOLAMINE	13961-86-9
112	OXALIC ACID	144-62-7
113	OXYTETRACYCLINE HYDROCHLORIDE	2058-46-0
114	PENTACHLOROPHENOL, DOWICIDE EC-7	87-86-5
115	PHENACETIN	62-44-2
116	PHENFORMIN HYDROCHLORIDE	834-28-6
117	N-PHENYL-2-NAPHTHYLAMINE	135-88-6
118	N-PHENYL-P-PHENYLENEDIAMINE	101-54-2
119	1-PHENYL-2-THIOUREA	103-85-5
120	PHTHALIC ANHYDRIDE	85-44-9
121	POLYSORBATE 80 (GLYCOL)	9005-65-6
122	POTASSIUM FLUORIDE	7789-23-3
123	PROBENECID	57-66-9
124	PROMETHAZINE HYDROCHLORIDE	58-33-3
125	PROPIONIC ACID	79-09-4
126	PROPIONIC ACID, METHYL ESTER	554-12-1
127	PROPYLENE	115-07-1
128	1,2-PROPYLENE OXIDE	75-56-9
129	PYRILAMINE MALEATE	59-33-6
130	QUERCETIN	117-39-5
131	SEBACIC ACID	111-20-6
132	SODIUM AZIDE	26628-22-8
133	SODIUM FLUORIDE	7681-49-4
134	STEARIC ACID	57-11-4
135	SUCCINIC ACID	110-15-6
136	SUCCINIC ANHYDRIDE	108-30-5
137	SUCROSE	57-50-1
138	SULFAMETHAZINE	57-68-1

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TABLE 6

CHEMICALS SELECTED TO BE TESTED FOR MUTAGENICITY IN L5178Y MOUSE LYMPHOMA CELLS IN FY 1987

SEQ. NO.	CHEMICAL	CAS NO.
139	3-SULFOLENE	77-79-2
140	TALC	14807-96-6
141	1,1,2,2-TETRACHLOROETHANE	79-34-5
142	TITANOCENE DICHLORIDE	1271-19-8
143	TOLAZAMIDE	1156-19-0
144	TOLBUTAMIDE	64-77-7
145	2,5-TOLUENEDIAMINE SULFATE	6369-59-1
146	TRIAMTERENE	396-01-0
147	TRIPELENNAMINE HYDROCHLORIDE	154-69-8
148	TRIS(2-CHLOROETHYL) PHOSPHATE	115-96-8
149	L-TRYPTOPHAN	73-22-3
150	TURMERIC, OLEORESIN (CURCUMIN)	8024-37-1
151	N-VALERIC ACID	109-52-4
152	VINYLIDENE CHLORIDE	75-35-4
153	WOLLASTONITE CALCIUM SILICATES	13983-17-0

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TABLE 7

CHEMICAL TEST RESULTS FOR CYTOGENETIC EFFECTS IN
CHINESE HAMSTER OVARY CELLS IN FY 1986

SEG. NO.	CHEMICAL	RESULTS * **		CAS NO.
		CA	SCE	
1	ACETOHEXAMIDE	-	-	968-81-0
2	ALDICARB OXIME	-	-	1646-75-9
3	ANTHRALIN	-	-	1143-38-0
4	L-ASCORBIC ACID	-	+	50-81-7
5	2-BIPHENYLAMINE HYDROCHLORIDE	+W	-	2185-92-4
6	CALCIUM CYANAMIDE	-	-	156-62-7
7	4-CHLORO-M-PHENYLENEDIAMINE	+	+	5131-60-2
8	4-CHLORO-O-PHENYLENEDIAMINE	+	+	95-83-0
9	1-CHLORO-2-PROPANOL	+	+	127-00-4
10	C. I. ACID ORANGE 10	+	-	1936-15-8
11	C. I. ACID RED 14	-	-	3567-69-9
12	C. I. SOLVENT YELLOW 14	-	+	842-07-9
13	CYTEMBENA	+	+	21739-91-3
14	D & C RED NO. 9	-	-	5160-02-1
15	D & C YELLOW NO. 11	+	+	8003-22-3
16	DIALLYL PHTHALATE	+W	+	131-17-9
17	2,4-DIAMINOTOLUENE	+	+	95-80-7
18	1,2-DIBROMOETHANE (ETHYLENE DIBROMIDE)	+	+	106-93-4
19	2,6-DIISOCYANATOTOLUENE	+	+	91-08-7
20	N-(1,3-DIMETHLBUTYL)-N-PHENYL-P-PHENYLENEDIAMINE	-	-	793-24-8
21	N,N-DIMETHYL-P-PHENYLENEDIAMINE	-	+	99-98-9
22	N,N'-DIPHENYL-P-PHENYLENEDIAMINE	-	+	74-31-7
23	N,N'-DI-SEC-BUTYL-P-PHENYLDIAMINE	-	-	101-96-2
24	ETHYL METHACRYLATE	-	+	97-63-2
25	FD & C YELLOW NO. 6	-	?	2783-94-0
26	FORMULATED FENAMINOSULF	-	+	140-56-7
27	MALAOXON	-	+	1634-78-2
28	MELPHALAN	+	+	148-82-3
29	DL-MENTHOL	-	-	15356-70-4
30	4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE	+	+	13552-44-8
31	METHYLETHYL KETONE	-	-	78-93-3
32	2-NAPHTHYLAMINE	+	+	91-59-8
33	P-NITROBENZOIC ACID	+	+	62-23-7
34	P-NITROHIPPURIC ACID	-	-	2645-07-0
35	2-NITRO-P-PHENYLENEDIAMINE	+	+	5307-14-2
36	5-(4-NITROPHENYL)-2,4-PENTADIEN-1-AL (NPPD)	-	-	2608-48-2
37	PENTACHLORONITROBENZENE	+	+	82-68-8
38	PHENFORMIN HYDROCHLORIDE	-	-	834-28-6
39	M-PHENYLENEDIAMINE	+	+	108-45-2
40	N-PHENYL-2-NAPHTHYLAMINE	-	?	135-88-6
41	N-PHENYL-1-NAPHTHYLAMINE	-	+	90-30-2
42	PROPYL GALLATE	+	+	121-79-9

* + = POSITIVE, - = NEGATIVE, ? = EQUIVOCAL, W = WEAK RESPONSE
** RESULTS SEPARATED BY COMMAS REPRESENT MULTIPLE TESTS
CA = CHROMOSOME ABERRATIONS, SCE = SISTER CHROMATID EXCHANGES

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TABLE 7

CHEMICAL TEST RESULTS FOR CYTOGENETIC EFFECTS IN CHINESE HAMSTER OVARY CELLS IN FY 1986

SEQ. NO.	CHEMICAL	RESULTS *		CAS NO.
		CA	** SCE	
43	QUINOLINE	+	+	91-22-5
44	SELENIUM SULFIDE	+	+	7446-34-6
45	STANNOUS CHLORIDE	+	+	7772-99-8
46	SULFISOXAZOLE	−	+	127-69-5
47	1, 2, 3, 4-TETRACHLOROBENZENE	−	+	634-66-2
48	1, 2, 3, 5-TETRACHLOROBENZENE	−	−	634-90-2
49	1, 2, 4, 5-TETRACHLOROBENZENE	−	−	95-94-3
50	2, 3, 5, 6-TETRACHLOROPHENOL	+	+	935-95-5
51	TOLAZAMIDE	−	−	1156-19-0
52	TOLBUTAMIDE	−	+	64-77-7
53	2, 6-TOLUENEDIAMINE DIHYDROCHLORIDE	+	+	15481-70-6
54	2, 5-TOLUENEDIAMINE SULFATE	+	+	6369-59-1
55	2, 4-TOLUENE DIISOCYANATE	−	?	584-84-9
56	2, 3, 4-TRICHLOROPHENOL	+	+	15950-66-0
57	2, 3, 6-TRICHLOROPHENOL	+	−	933-75-5
58	3, 4, 5-TRICHLOROPHENOL	−	−	609-19-8
59	2, 4, 5-TRIMETHYLANILINE	+	+	137-17-7
60	TRIS(2-ETHYLHEXYL)PHOSPHATE	−	−	78-42-2
61	1, 3, 5-TRIS(2-HYDROXYETHYL)TRIAZINE-2, 4, 6-TRIONE	−	−	839-90-7
62	L-TRYPTOPHAN	−	−	73-22-3
63	ZIRAM	+	−	137-30-4

* + = POSITIVE, − = NEGATIVE, ? = EQUIVOCAL, W = WEAK RESPONSE
** RESULTS SEPARATED BY COMMAS REPRESENT MULTIPLE TESTS
CA = CHROMOSOME ABERRATIONS, SCE = SISTER CHROMATID EXCHANGES

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TABLE 8

CHEMICALS SELECTED TO BE TESTED FOR CYTOGENETIC EFFECTS IN CHINESE HAMSTER OVARY CELLS IN FY 1987

SEQ. NO.	CHEMICAL	CAS NO.
1	ACETALDEHYDE	75-07-0
2	ACETAMINOPHEN	103-90-2
3	ACETONE	67-64-1
4	4-ACETYL PYRIDINE	1122-54-9
5	ACRYLAMIDE	79-06-1
6	1-AMINO-2, 4-DIBROMOANTHRAQUINONE	81-49-2
7	3-AMINO-4-ETHOXYACETANILIDE	17026-81-2
8	3-AMINO-9-ETHYLCARBAZOLE	6109-97-3
9	1-AMINO-2-METHYLANTHRAQUINONE	82-28-0
10	4-AMINO-2-NITROPHENOL	119-34-6
11	2-AMINO-5-NITROTHIAZOLE	121-66-4
12	AMPHETAMINE SULFATE	60-13-9
13	AMPHOTERICIN B	1397-89-3
14	AROCLOR 1254	11097-69-1
15	AZINPHOSMETHYL	86-50-0
16	BENZONITRILE	100-47-0
17	BENZO(A)PYRENE	50-32-8
18	BENZYL CHLORIDE	100-44-7
19	N, N'-BIS(1, 4-DIMETHYLPENTYL)-P-PHENYLENEDIAMINE	3081-14-9
20	1, 3-BUTADIENE	106-99-0
21	N-BUTANE	106-97-8
22	N-BUTYL ACRYLATE	141-32-2
23	T-BUTYLHYDROQUINONE	1948-33-0
24	CAPTAN	133-06-2
25	CARBENDAZIM	10605-21-7
26	CARBON DISULFIDE	75-15-0
27	CARBON TETRACHLORIDE	56-23-5
28	D-CARVONE	2244-16-8
29	CASTOR OIL	8001-79-4
30	CHLORINATED PARAFFINS: C12, 60% CHLORINE	63449-39-8
31	CHLOROACETOPHENONE (CN)	532-27-4
32	CHLOROPICRIN	76-06-2
33	CHLOROPRENE	126-99-8
34	C. I. ACID ORANGE 3	6373-74-6
35	C. I. DIRECT BLACK 38	1937-37-7
36	C. I. DISPERSE BLUE 1	2475-45-8
37	C. I. PIGMENT RED 3	2425-85-6
38	C. I. PIGMENT RED 23	6471-49-4
39	C. I. VAT YELLOW 4	128-66-5
40	COCONUT DIETHANOLAMIDE	68603-42-9
41	M-CRESIDINE	102-50-1
42	P-CRESIDINE	120-71-8
43	CUPFERRON	135-20-6
44	CYCLOPHOSPHAMIDE	50-18-0
45	CYCLOSPORIN A	59865-13-3
46	2, 4-DIAMINOANISOLE SULFATE	39156-41-7

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TABLE 8

CHEMICALS SELECTED TO BE TESTED FOR CYTOGENETIC EFFECTS IN CHINESE HAMSTER OVARY CELLS IN FY 1987

SEQ. NO.	CHEMICAL	CAS NO.
47	4,4'-DIAMINO-2,2'-STILBENEDISULFONIC ACID	81-11-8
48	2,3-DIBROMO-1-PROPANOL	96-13-9
49	CIS-DICHLORODIAMINE PLATINUM	15663-27-1
50	2,7-DICHLORODIBENZO-P-DIOXIN	33857-26-0
51	DICHLORODIPHENYLTRICHLOROETHANE	50-29-3
52	1,2-DICHLOROETHANE	107-06-2
53	1,1-DICHLOROETHANE	75-34-3
54	DICHLOROMETHANE (METHYLENE CHLORIDE)	75-09-2
55	2,3-DICHLOROPROPYLENE	78-88-6
56	DI(P-ETHYLPHENYL)DICHLOROETHANE	72-56-0
57	N,N-DIETHYL-P-PHENYLENEDIAMINE	93-05-0
58	3,4-DIHYDROCOUMARIN	119-84-6
59	3,3'-DIMETHOXYBENZIDINE-4,4'-DIISOCYANATE	91-93-0
60	4,4'-DIMETHOXYDIPHENYLAMINE	101-70-2
61	DIMETHYL PHTHALATE	131-11-3
62	DIMETHYL SULFOXIDE	67-68-5
63	N,N'-DI-2-NAPTHYL-P-PHENYLENEDIAMINE	93-46-9
64	4,4'-DIOCTYLDIPHENYLAMINE	101-67-7
65	DOXYLAMINE SUCCINATE	562-10-7
66	ELLAGIC ACID	476-66-4
67	ENDOSULFAN	115-29-7
68	EPINEPHRINE	51-43-4
69	ETHIONAMIDE	536-33-4
70	ETHYL ACETATE	141-78-6
71	ETHYL CHLORIDE	75-00-3
72	ETHYLENE GLYCOL MONOBUTYL ETHER (EGMBE)	111-76-2
73	ETHYLENE OXIDE	75-21-8
74	2-ETHYLHEXANOL	104-76-7
75	FLUOMETURON	2164-17-2
76	FLURAZEPAM	17617-23-1
77	FUMARIC ACID DINITRILE	EMTDP-73
78	FURAN	110-00-9
79	FUROSEMIDE	54-31-9
80	HC RED 3	2871-01-4
81	HEXACHLOROBENZENE	118-74-1
82	HEXACHLOROCYCLOPENTADIENE	77-47-4
83	HEXACHLOROPHENE	70-30-4
84	N-HEXANE	110-54-3
85	1,6-HEXANEDIAMINE, DIHYDROCHLORIDE	6055-52-3
86	2-HYDROXY-4-METHOXYBENZOPHENONE	131-57-7
87	IODINATED GLYCEROL	5634-39-9
88	ISOPENTANE	78-78-4
89	ISOPRENE	78-79-5
90	P-ISOPROPOXYDIPHENYLAMINE	101-73-5
91	N-ISOPROPYL-N'-PHENYL-P-PHENYLENEDIAMINE	101-72-4
92	LAURIC ACID DIETHANOLAMINE CONDENSATE	120-40-1

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TABLE 8

CHEMICALS SELECTED TO BE TESTED FOR CYTOGENETIC EFFECTS IN CHINESE HAMSTER OVARY CELLS IN FY 1987

SEQ. NO.	CHEMICAL	CAS NO.
93	MALTOL	118-71-8
94	6-METHOXY-2-BENZOTHIAZOLAMINE	1747-60-0
95	2-METHOXYETHYL ACETATE	110-49-6
96	8-METHOXYPSORALEN	298-81-7
97	METHYL ETHYL KETOXIME	96-29-7
98	N-METHYLOLACRYLAMIDE	924-42-5
99	6-METHYLQUINOLINE	91-62-3
100	8-METHYLQUINOLINE	611-32-5
101	7-METHYLQUINOLINE	612-60-2
102	ALPHA-METHYLSTYRENE	98-83-9
103	NAPHTHALENE	91-20-3
104	1-NAPHTHYLAMINE	134-32-7
105	NITHIAZIDE	139-94-6
106	4-NITRO-1,3-BENZENEDIAMINE	5131-58-8
107	O-NITROBENZOIC ACID	552-16-9
108	P-NITROBENZOYL CHLORIDE	122-04-3
109	NITROFURANTOIN	67-20-9
110	N-NITROSODIPHENYLAMINE	86-30-6
111	P-NITROSODIPHENYLAMINE	156-10-5
112	BETA-NITROSTYRENE	102-96-5
113	OCHRATOXIN A	303-47-9
114	OLEIC ACID DIETHANOLAMINE	13961-86-9
115	OXAZEPAM	604-75-1
116	PENTAERYTHRITOL TETRANITRATE	78-11-5
117	PHENESTERIN	3546-10-9
118	O-PHENYLENEDIAMINE	95-54-5
119	PICRIC ACID	88-89-1
120	POLYSORBATE 80 (GLYCOL)	9005-65-6
121	PROBENECID	57-66-9
122	PROPIONITRILE	107-12-0
123	PROPYLENE	115-07-1
124	PYRILAMINE	91-84-9
125	QUERCETIN	117-39-5
126	RHODAMINE 6G	989-38-8
127	ROXARSONE	121-19-7
128	SALICYLAZOSULFAPYRIDINE	599-79-1
129	SCOPOLAMINE HYDROBROMIDE	114-49-8
130	SODIUM AZIDE	26628-22-8
131	SODIUM XYLENESULFONATE	1300-72-7
132	STYRENE	100-42-5
133	SULFAMETHAZINE	57-68-1
134	TETRACHLORODIPHENYLETHANE	72-54-8
135	2,3,4,6-TETRACHLOROPHENOL	58-90-2
136	2,3,4,5-TETRACHLOROPHENOL	4901-51-3
137	TETRACHLOROPHTHALIC ANHYDRIDE	117-08-8
138	TETRACHLORVINPHOS	961-11-5

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TABLE 8

CHEMICALS SELECTED TO BE TESTED FOR CYTOGENETIC EFFECTS IN CHINESE HAMSTER OVARY CELLS IN FY 1987

SEQ. NO.	CHEMICAL	CAS NO.
139	TETRAFLUOROETHYLENE	116-14-3
140	TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM SULFATE	55566-30-8
141	N, N, N', N'-TETRAMETHYL-P-PHENYLENEDIAMINE	100-22-1
142	TETRANITROMETHANE	509-14-8
143	4, 4'-THIODIANILINE	139-65-1
144	TITANOCENE DICHLORIDE	1271-19-8
145	2, 4-&2, 6-TOLUENE DIISOCYANATE	26471-62-5
146	TRIALLYL ISOCYANURATE	1025-15-6
147	1, 1, 2-TRICHLOROETHANE	79-00-5
148	2, 3, 5-TRICHLOROPHENOL	933-78-8
149	1, 3, 5-TRIGLYCIDYL ISOCYANURATE	2451-62-9
150	TRIMELLITIC ANHYDRIDE	552-30-7
151	TRIMETHYLPHOSPHATE	512-56-1
152	TRIS(2-ETHYLHEXYL) ESTER PHOSPHOROUS ACID	301-13-3
153	TURMERIC, OLEORESIN (CURCUMIN)	8024-37-1
154	URETHANE	51-79-6
155	VALIUM	439-14-5
156	WOLLASTONITE CALCIUM SILICATES	13983-17-0
157	XYLENES, COMMERCIAL MIXTURE	1330-20-7

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NCTR DIVISION OF GENETIC TOXICOLOGY

UTILIZATION OF THE PRIMARY HEPATOCYTE/DNA REPAIR SYSTEM TO DETECT POTENTIAL GENOTOXICITY OF NTP CHEMICALS

Introduction -- It is known that DNA is the target for various cytotoxic, mutagenic, and carcinogenic chemicals. It is thought that a majority of chemical carcinogens or their metabolites are electrophiles that react with cellular nucleophiles such as nucleic acids and proteins. One result of nucleic acid binding is DNA repair. This is accomplished by excision of the adduct and subsequent polymerization and ligation of the DNA strand. One method for detecting DNA repair is the use of autoradiographic techniques to measure labeled thymidine incorporation into DNA of mammalian cells outside of the normal phase of DNA synthesis (unscheduled DNA synthesis, UDS). The system used in this project is the primary hepatocyte/DNA repair system, in which the cells are capable of metabolically activating many precarcinogens and premutagens to their active forms allowing measurement of UDS in the same cells that activate the test chemicals. The objective of this cooperative project with NIEHS/NTP was to test code NTP-selected chemicals in the primary hepatocyte/DNA repair system.

Experimental Design -- The standard protocol used primary hepatocytes isolated following in situ perfusion of rat livers with collagenase. The hepatocytes were exposed for 18-24 hours at 37°C to a series of concentrations (dependent upon solubility) of the test chemical in medium containing ^{3}H-thymidine. Following incubation, fixation of the cells, and autoradiography, the cells were stained with Giemsa and the grains in the emulsion over the nuclei and cytoplasm were counted with an electronic counter.

2-Acetylaminofluorene (2-AAF), the positive control, was used to monitor the metabolic state of the hepatocyte preparation. Depending upon the nature of the chemical being evaluated, the negative control was the solvent used to dissolve the chemical and if the solvent was organic, e.g., DMSO, ethanol, or acetone, the final concentration did not exceed one percent. Dosage selection for the UDS assay was based on the solubility of the chemical and cytotoxic information obtained either from the NTP or based on preliminary cytotoxicity testing. A concentration which exhibited a cytotoxic response (or the highest soluble concentration, in the absence of cytotoxicity) was selected as the highest concentration for the UDS assay and the remaining four doses were selected over a 2-logarithm range.

The test agent was considered to produce a positive finding if the results demonstrated a concentration-related, statistically significant increase in UDS over negative control values and/or a reproducible, statistically significant increase in UDS at one concentration. A negative conclusion was reached in the absence of a positive response, as defined above, when the test compound was tested to cytotoxic levels or to the limits of solubility.

FY 1986 ACCOMPLISHMENTS

One-hundred four chemicals were received and solubility characteristics defined. Cells have been exposed to 84 of the chemicals. Eighty-four chemicals have been completely assessed (including repeats from FY 1985), while five are undergoing re-analysis. (CONTACT PERSON: Dr. D.A. Casciano)

FY 1987 PROGRAM PLANS

The final report for this project will be completed and submitted to the NTP.

NIOSH

The NIOSH program in cellular and genetic toxicology, directed at assessing genotoxic risks in the workplace, is carried out by the Division of Respiratory Disease Studies. Potentially mutagenic airborne contaminants, ranging from individual chemical substances to complex mixtures of chemicals, may be present in certain occupational settings. Chemical manufacturing, coal gasification and liquefaction, underground mining using diesel equipment, and coke ovens are examples of industries and processes where workplace exposures are potentially hazardous. Many of these industries and processes produce mixtures containing hundreds of chemical compounds including polynuclear aromatic hydrocarbons, organic amines, and oxygenated and nitrated organic substances. To protect workers from potential mutagenic and associated risks, it is desirable to evaluate worksites for the presence of genotoxic substances and to monitor employees for the occurrence of genotoxic events. By monitoring plant personnel and the workplace environment, heretofore unidentified genotoxic agents may be detected and proper procedures to safeguard workers from exposure to these industrial by-products could be adopted and would presumably benefit the health of workers and their offspring. Five projects aimed at assessing genotoxic risks to workers are in various stages of development and application.

FY 1986 ACCOMPLISHMENTS

Validation of the Salmonella Arabinose Resistant Assay -- In a previous study, the arabinose resistant mutagenicity assay system was shown to be equal in mutagenic sensitivity to the Ames (*Salmonella*) assay. The arabinose assay system has been further evaluated with volatile mutagens and/or carcinogens, including methyl methanesulfonate, ethyl methanesulfonate, dimethylnitrosamine, propylene oxide, and complex mixtures such as tobacco snuff and chewing tobacco. The studies showed that all tested chemicals exhibited a dose-response for induction of mutations in the arabinose assay system. These results further indicate that the arabinose-resistant assay is a sensitive system for the detection of different types of mutagens. (CONTACT PERSON: Dr. W-Z. Whong)

Methodology for Workplace Mutagenic Monitoring -- The recently developed SOS chromotest appears to be a rapid and sensitive assay system for detecting DNA-damaging agents by monitoring SOS responses. Efforts have been made to determine whether this system can detect the genotoxicity of environmental complex mixtures. In this system, the SOS function induced by genotoxicants is detected by a colorimetric measurement of b-galactosidase in tester cells. Since most complex mixtures show a prominent color, we modified the assay procedures by (1) a 10-fold post-treatment dilution and (2) a 2-hour post-incubation. The post-treatment dilution may eliminate the possible false positive due to the color of test substances, while the post-incubation may increase the sensitivity of detection. With the modified methods, the SOS chromotest was tested with a variety of complex mixtures (i.e., diesel emission, airborne particles, coal dust, cigarette condensates and smokeless tobaccos). All tested samples showed a positive SOS response, indicating that the SOS chromotest has potential for the detection of genotoxicants in the workplace. (CONTACT PERSON: Dr. W-Z. Whong)

Evaluation of Urine Mutagenesis Assay -- In collaboration with Dr. Robert Hoy at West Virginia University Medical School, studies were conducted to compare the mutagenic activity of urine samples from nurses working with or not working with cytotoxic drugs. The Ames *Salmonella*/microsomal assay was used as a test system. The results indicate that nurses who are using gloves when preparing solutions for chemotherapy on an open counter and administering the solutions do not have a detectable level of mutagens in their urine. (CONTACT PERSON: Dr. T. Ong)

In Vivo and Partial In Vivo Cytogenetic Studies -- Sister chromatid exchange and chromosomal aberration analyses have been used to monitor human populations for genotoxic exposure to chemical substances. These monitoring techniques involve collection of blood and/or bone marrow from the exposed subjects and culturing cells for one or two cell cycles with various treatments in culture. The results obtained from such *in vivo/in vitro* studies may lead to an over or under estimation of the damage that could occur *in vivo*. In this study, using a mouse model, the *in vivo/in vitro* cytogenetic assays were compared with similar *in vivo* systems in bone marrow and spleen cells treated with cyclophosphamide (CPA). The results indicate a significant difference in CPA-induced cytogenetic endpoints between *in vivo* and *in vivo/in vitro* conditions in both tissues. However, linear relationships were found between CPA dose and cytogenetic endpoint analyzed under both conditions. Based on these results it appears that the *in vivo/in vitro* assay is a useful technique for indicating potential *in vivo* damage of chemicals. (CONTACT PERSON: Dr. T. Ong)

Antimutagenic Activity of Chlorophyllin -- The level of mutagens and carcinogens may be reduced in our environment and workplaces, but it is unlikely that the exposure of humans to these agents can be completely eliminated. It is important, therefore, to identify agents that can counteract or eliminate mutagens and carcinogens and that have a practical use in humans. In this project we found that chlorophyllin, the sodium and copper salt of chlorophyll, was highly effective against the mutagenicity (90-100% inhibition) of airborne particles, coal dust, diesel emission particles, and cigarette smoke. The mutagenicity in *Salmonella typhimurium* of tobacco snuff and chewing tobacco was inhibited 75-80%. These results indicate that chlorophyllin is potentially useful as an antimutagenic agent. (CONTACT PERSON: Dr. T. Ong)

FY 1987 PROGRAM PLANS

Methodology for Workplace Mutagenic Monitoring - Validation of the SOS chromotest will be continued. Efforts will be made to incorporate the SOS chromotest into the *in situ* test system for monitoring of genotoxic agents in the workplace. (CONTACT PERSON: Dr. W-Z. Whong)

Multiple Endpoint Genotoxicity Assay System in Lung Cells -- Development of a system for studying the genotoxicity of industrial chemicals in lung cells using multiple genetic endpoints will be initiated. The unscheduled DNA synthesis assay system using alveolar macrophages and/or other primary lung cells will be established. (CONTACT PERSON: Dr. W-Z Whong)

In Vitro and In Vivo Cytogenetic Studies -- Due to absorption, distribution and metabolism, chemicals found to be genotoxic in the *in vitro* short-term tests may not be genotoxic *in vivo*. For determining the potential hazard of chemicals to the exposed workers and the utility of short-term tests, *in vitro* and *in vivo* comparative studies using the same tissue or similar cell types should be performed. Bone marrow and spleen cells have been used extensively for the *in vivo* cytogenetic studies. In this project, *in vitro* cytogenetic assay systems using bone marrow and spleen cells will be established. Comparative *in vivo* and *in vitro* studies for selected occupationally related chemicals will be performed. (CONTACT PERSON: Dr. T. Ong)

Antimutagenic Activity of Chlorophyllin -- The antimutagenic activity of chlorophyllin against chemicals and complex mixtures will be tested with other assay systems, and will be compared with the activities of several known antimutagens including vitamins (A, C and E), retinoic acid and b-carotene. (CONTACT PERSON: Dr. T. Ong)

CARCINOGENESIS RESEARCH AND APPLIED STUDIES

Despite considerable advances in our understanding of cancer biology, and the development of more predictive short-term assays for genotoxic potential, the two-year exposure studies in rodents remain the most definitive method for identifying chemical carcinogens. All chemicals recognized as being carcinogenic to humans have also been shown to cause cancer in laboratory animals under appropriate experimental conditions; the identification of chemical carcinogens in animals provides guidance as to potential chemical hazards in humans, and forms the basis for the hazard identification step of the risk assessment and risk management processes. These findings are valuable in the important area of preventing human cancers. Thus, the NTP accepts the concept that chemicals found to cause cancer in animals should be considered potentially capable of causing cancer in humans. This concept has been endorsed widely, especially in recent publications by the Office of Technology Assessment (1981), the Office of Science and Technology Policy (1985), and the International Agency for Research on Cancer (1985).

To identify those potential chemical carcinogens of most importance to human health, the NTP evaluates large production volume chemicals with a high probability of human exposure. More specifically, test chemicals are chosen on the bases of the extent (and level) of human exposure, volume of production, nature of the use, availability of toxicologic data (or lack thereof), suspected biological activity (such as mutagenicity), and chemical structure. Although carcinogenic activity is a major endpoint, other important studies are commonly included to more adequately define chemical toxicities and their cause or causes. Chemical disposition (absorption, distribution, metabolism, excretion), genetic toxicology, assessment of effects on fertility and reproduction, target organ characterization (especially in prechronic studies), immunotoxicity, and clinical pathology (e.g., clinical chemistries, hematology, urinalyses) are examples of studies performed in addition to the two-year chronic toxicology and carcinogenesis studies.

The two-year carcinogenicity study in rodents, although modified extensively by the NTP, remains similar in general protocol to that developed largely by the NCI. A typical design employs both sexes of rats (usually the Fischer 344 inbred strain) and of mice (usually the $B6C3F_1$ hybrid strain), and administration of multiple doses (usually three, plus vehicle and/or untreated concurrent controls) of the chemical to groups of at least 50 animals for approximately two years. The animals are generally 6-18 weeks of age at initiation of exposure to a chemical. Dose ranges for the chronic (usually two-year) study are based on estimates of non-lethal, minimally toxic doses, dose-response curves, pharmacokinetic considerations, probable levels of human exposure and other relevant factors. Generally, the lower doses are some fraction of the highest dose. In addition to the two-year exposure groups, some animals may be killed after 12, 15, or 18 months of exposure to evaluate chronic toxicity before the onset of senescent changes. For some chemicals, the chemical administration is stopped ("Stop Studies") after a specific period of exposure ranging from 3 to 21 months and regression/progression of lesions is followed during the remaining period of the study by histopathologic evaluation of tissues from the animals sacrificed at various intervals.

As developed some years ago, the prechronic studies (generally 14-day and 90-day studies) were carried out principally to aid in dose selection for chronic carcinogenicity studies. However, the NTP has broadened the toxicological characterization, expanding the study to detect chemical toxicity. The prechronic toxicity studies, along with chemical disposition and genetic toxicity information, are used to better tailor the chronic study design to the chemicals being evaluated, as well as to provide relevant toxicologic information. Indeed, the prechronic and other studies often identify target organ toxicity for further study. Such data are also used to determine the relative priority of candidate chemicals for chronic study, as well as the extent and level of detail of the study design.

The majority of the NTP prechronic and chronic studies are managed by the NIEHS component. In addition, some studies are conducted by the NCTR and the NIOSH components. NCTR managed studies are most frequently done on chemicals having particular relevance to the FDA. The NIOSH-managed studies usually involve substances and routes of administration associated with acknowledged occupational exposures and often are selected because of some indication of potential human hazard.

NIEHS

FY 1986 ACCOMPLISHMENTS

PRECHRONIC AND TWO-YEAR STUDIES

Completed Studies -- During FY 1986, 19 two-year studies were completed and the draft Technical Reports of the findings were approved by the NTP Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts (Peer Review Panel) (Tables 9 and 10). The levels of evidence of carcinogenicity (see below) for each sex/species group are summarized in Table 9. More complete information about the chemical and the study is given in Table 10. Data audits were completed prior to peer review for all of these studies and a summary of the audit finding is included in the draft and final Technical Reports. NTP Technical Reports may be obtained free of charge while supplies last from the NTP Public Information Office, MD B2-04, P. O. Box 12233, Research Triangle Park, NC 27709 Phone: (919) 541-3991; FTS 629-3991.

Levels of Evidence -- Categories of interpretive conclusions adopted by the NTP in FY 1983 continued to be used in the Technical Reports to describe the strength of experimental evidence for each individual study result or experiment -- that is, for male rats, female rats, male mice, and female mice. Five categories or levels have been used to maintain consistency in defining evidence of carcinogenicity, being -- Clear Evidence of Carcinogenicity, Some Evidence of Carcinogenicity, Equivocal Evidence of Carcinogenicity, No Evidence of Carcinogenicity, and Inadequate Study of Carcinogenicity. The levels of evidence have been included in the Note to the Reader section located on page 2 of each Technical Report. Since their adoption (from June 1983 through March 1986), they have been used to evaluate 52 toxicology and carcinogenesis studies representing 192 separate experiments. There was consensus among the Peer Review Panel members that the levels as used for the Technical Reports were an advancement. More specifically, there was concurrence by the Panel with the level of evidence proposed by the NTP staff on 185 of the 192 experiments.

During FY 1986, the Program in agreement with the Board of Scientific Counselors decided to reevaluate the set of five categories and examine each definition to determine whether improvements could be made. Possible changes were discussed with the Board and Peer Review Panel in public sessions. The major change proposed centered on a more explanatory narrative in the Note to the Reader section and inclusion of a list of key factors that could allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals in consideration of the appropriate level of evidence. A revised Note was placed in the Federal Register and comments requested within 45 days. Numerous comments were received and reviewed by staff and members of the Board and Panel. Proposed modifications were discussed at length by the Board in public session on March 25, 1986, with adequate time allowed for public comment. As a result, several changes were recommended by the Board and accepted by the Program.

A revised Note to the Reader, now titled Explanation of Levels of Evidence, will appear in all future Toxicology and Carcinogenesis Studies Technical Reports evaluated by the Panel beginning with reports reviewed by the Panel on August 19, 1986. The section appears immediately after the Abstract section of the Report. The current Explanation of Levels of Evidence section was also published in the Federal Register Vol. 51, No. 66, pp. 11843-11844, April 7, 1986.

The revised levels of evidence are:

- Clear Evidence of Carcinogenic Activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.

- Some Evidence of Carcinogenic Activity is demonstrated by studies that are interpreted as showing a chemically related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.

- Equivocal Evidence of Carcinogenic Activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemically related.

- No Evidence of Carcinogenic Activity is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.

- Inadequate Study of Carcinogenic Activity is demonstrated by studies that because of major qualitative or quantitative limitations cannot be interpreted as valid for showing either the presence or absence of a carcinogenic effect. (CONTACT PERSON: Dr. L. G. Hart)

Status of Ongoing Studies -- There were 43 studies (36 chemicals) in the prechronic phase of toxicology and carcinogenesis studies (Table 11) and 154 studies (139 chemicals) in the chronic phase (usually two-year) (Table 12) at the end of FY 1986. Those in the chronic phase include studies that are in the histopathology and report preparation phases.

All prechronic and long-term toxicology and carcinogenesis studies are under direct NTP management, and most are awarded through a master agreement contracting mechanism whereby laboratories and their personnel are qualified for standard protocols and in each of various special study areas prior to announcing requests for specific proposal (RFPs). This provides a group of qualified laboratories to compete for awards to do studies on chemicals according to specific protocols.

As in previous years, the NTP General Statement of Work (SOW) for the Conduct of Toxicity and Carcinogenicity Studies in Rodents is being reviewed and updated to incorporate refinements in study design and changes in related guidelines or rules. Sample protocols for use by chemical managers in the development of protocols for studies of specific chemicals have been updated in concert with the revised SOW.

Master Agreement Awards were made to four new laboratories following successful competition in response to a Master Agreement Announcement. The Master Agreement Awards enable the laboratories to compete for Master Agreement Orders (MAO) to conduct studies on specific chemicals. Plans are in progress for the issuance of another Master Agreement Announcement in FY 1987. Two of the four laboratories recently added to the pool have successfully competed for MAO/RFPs. The other two have not yet competed.

Twenty-seven Master Agreement Order RFPs were issued for awards in FY 1986. Six of the RFPs were cancelled: five for convenience of the Government in response to budgetary constraints and one due to no offerors. The remaining awards completed or pending cover a range of prechronic and/or chronic studies on twenty-four different chemicals. Eight of the 24 chemicals are Superfund chemicals. One of the 24 chemicals was a readvertisement of studies awarded in FY 1984 and cancelled for default.

Plans are underway for FY 1987 awards taking into consideration probable continued budgetary constraints. An estimated seven MAO/RFPs have been or will be issued in FY 1986 for award during the first and second quarter of FY 1987. (CONTACT PERSON: Dr. M.L. Vernon)

Other Long-Term Studies -- Chronic toxicity and carcinogenicity studies of a polybrominated biphenyl mixture (Firemaster FF-10), diphenylhydantoin (phenytoin) and ethylenethiourea have been completed in animals treated during the post-weaning phase of life and in other animals treated in utero (gestation), neonatally, and post-weaning. The objective of these studies was to determine whether gestational and neonatal exposure to the chemicals can alter susceptibility to chronic toxicologic and carcinogenic effects. (CONTACT PERSON: Dr. R. Chhabra)

Human Carcinogen Data Base -- There are approximately 35 to 40 chemicals for which convincing evidence exists linking exposure to the development of cancer in humans. Several of these compounds have also produced carcinogenic responses in animal tests. However, this data base needs to be expanded before it will be possible to evaluate the adequacy of current methodologies for assessing carcinogenic potential. Therefore, NIEHS/NTP has begun a major initiative to characterize a selected group of these human carcinogens using current methods for studies in animals. The data generated by these studies will provide a basis for analyzing the response of current methodologies and serve as a reference base against which to compare the utility of emerging methods. (CONTACT PERSON: Dr. R. Irwin)

METHODS DEVELOPMENT AND VALIDATION

Long-Term Animal Assay Methodology -- Information is given in the Data Management and Analysis chapter.

Short-Term Carcinogenesis Assays -- Information is given in the Chemical Pathology chapter.

FY 1987 PROGRAM PLANS

PRECHRONIC AND TWO-YEAR STUDIES

For FY 1987, the NTP has scheduled 33 studies (30 chemicals plus a complex mixture) to begin the prechronic phase of the toxicology and carcinogenesis studies process (Table 13), and 12 studies (12 chemicals) to begin the chronic phase (Table 14). It is projected that 27 two-year studies (26 chemicals) will be completed and the draft reports will be peer reviewed in FY 1987 (Table 15). (CONTACT PERSON: Dr. L. G. Hart)

TABLE 9

SUMMARY OF STRENGTH OF EVIDENCE FOR CARCINOGENICITY IN NTP DRAFT TECHNICAL REPORTS PEER REVIEWED IN FY 1986

Chemical Name	CAS No.	Levels of Evidence*			
		MR	FR	MM	FM**
Ampicillin Trihydrate	7177-48-2	EE	NE	NE	NE
Boric Acid	10043-35-3	--	--	NE	NE
Bromodichloromethane	75-27-4	CE	CE	CE	CE
Chlorpheniramine Maleate	113-92-8	NE	NE	NE	NE
1,4-Dichlorobenzene	106-46-7	CE	NE	CE	CE
Dimethyl Methylphosphonate	756-79-6	SE	NE	IS	NE
Dimethylvinyl Chloride	513-31-1	CE	CE	CE	CE
1,2-Epoxybutane	106-88-7	CE	EE	NE	NE
Ethylene Oxide	75-21-8	--	--	CE	CE
Methyl Carbamate	598-55-0	CE	CE	NE	NE
Methyl Methacrylate	80-62-6	NE	NE	NE	NE
Oxytetracycline Hydrochloride	2058-46-0	EE	EE	NE	NE
Pentachloronitrobenzene	82-68-8	--	--	NE	NE
Phenylephrine Hydrochloride	61-76-7	NE	NE	NE	NE
Rotenone	83-79-4	EE	NE	NE	NE
Tetrakis (Hydroxymethyl) Phosphonium Chloride	124-64-1	NE	NE	NE	NE
Tetrakis (Hydroxymethyl) Phosphonium Sulfate	55566-30-8	NE	NE	NE	NE
Trichloroethylene***	79-01-6	IS	IS	--	--
Xylenes (Mixed)	1330-20-7	NE	NE	NE	NE

* Levels of Evidence
CE=clear evidence of carcinogenicity or carcinogenic activity
SE=some evidence of carcinogenicity or carcinogenic activity
EE=equivocal evidence of carcinogenicity or carcinogenic activity
NE=no evidence of carcinogenicity or carcinogenic activity
IS=inadequate study of carcinogenicity or carcinogenic activity

** MR=male rats; FR=female rats; MM=male mice; FM=female mice

*** Inadequate study in each of four rat strains-ACI, August, Marshall, and Osborne-Mendel

TABLE 10

NTP TOXICOLOGY AND CARCINOGENESIS STUDY RESULTS

NTP/TR REPORT CHEMICAL NAME CAS NUMBER	NO. — PEER REVIEW DATE	USE	ROUTE/DOSE	TESTING LABORATORY	NTP CHEMICAL MANAGER	RESULTS UNDER THE CONDITIONS OF THESE STUDIES
AMPICILLIN TRIHYDRATE 7177-48-2	NTP-85-172 TR-318 12/09/85	PHARMACEUTICAL	GAVAGE (CORN OIL) RATS—0, 750 OR 1,500 MG/KG; MICE—0, 1,500 OR 3,000 MG/KG 5 DAYS/WEEK FOR 103 WEEKS	SPRINGBORN INSTITUTE FOR BIORESEARCH	DR. J. K. DUNNICK	EQUIVOCAL EVIDENCE OF CARCINOGENICITY IN MALE F344/N RATS AS SHOWN BY MARGINALLY INCREASED INCIDENCE OF MONONUCLEAR CELL LEUKEMIA (5/50, 15/50, 14/50) AND INCREASED INCIDENCE OF PHEOCHROMOCYTOMAS OR MALIGNANT PHEOCHROMOCYTOMAS (COMBINED) OF THE ADRENAL GLAND MEDULLA (13/50, 16/50, 23/49). THERE WAS NO EVIDENCE OF CARCINOGENICITY IN FEMALE F344/N RATS OR B6C3F1 MICE OF EITHER SEX.
BORIC ACID 10043-35-3	NTP-85-307 TR-324 03/26/86	USED IN COSMETICS, MEDICINE, FABRICS, PAINT MANUFACTURING, CHEMISTRY, PHOTOGRAPHY, & METALLURGY	FEED: MICE - 0, 2,500, OR 5,000 PPM	EG&G MASON RESEARCH INSTITUTE	DR. M. P. DIETER	NO EVIDENCE OF CARCINOGENICITY FOR B6C3F1 MICE OF EITHER SEX.
BROMODICHLOROMETHANE 75-27-4	NTP-86-026 TR-321 08/19/86	CHEMICAL INTERMEDIATE	GAVAGE: RATS-0, .05 OR .10 G/KG; MICE- 0, .025, .05, .075 OR .15 G/KG	EG&G MASON RESEARCH INSTITUTE	DR. J. K. DUNNICK	CLEAR EVIDENCE OF CARCINOGENIC ACTIVITY IN F341/N RATS AS INDICATED BY INCREASED INCIDENCE OF KIDNEY TUBULAR CELL ADENOMAS (MALE: 0/50, 1/50, 5/50; FEMALE:0/50, 1/50, 6/50), KIDNEY TUBULAR CELL ADENOCARCINOMA (MALE: 0/50, 0/50, 10/50; FEMALE: 0/50, 0/50, 9/50), LARGE INTESTINE ADENOMATOUS POLYPS (MALE:0/50, 3/50, 33/50; FEMALE: 0/46, 0/50, 6/47). THERE IS CLEAR EVIDENCE OF CARCINOGENIC ACTIVITY IN B6C3F1 MICE AS INDICATED BY INCREASED INCIDENCE IN MALE MICE OF KIDNEY ADENOMA (1/49, 2/50, 6/50) AND KIDNEY ADENOCARCINOMA (0/49, 0/50, 4/50) AND IN FEMALE MICE OF HEPATOCELLULAR ADENOMA (1/50, 13/48, 23/50) AND HEPATOCELLULAR CARCINOMA (2/50, 5/48, 10/50).
CHLORPHENIRAMINE MALEATE 113-92-8	NTP-85-154 TR-317 12/09/85	ANTIHISTAMINE	GAVAGE (WATER) RATS-MALE 0,15 OR 30;FEMALE 0, 30 OR 60:MICE-MALE 0,25 OR 50;FEMALE 0,100 OR 200 MG/KG 5 DAY/WK 103 WK	BATTELLE COLUMBUS LABORATORIES	DR. R. L. MELNICK	NO EVIDENCE OF CARCINOGENICITY IN F344/N RATS OR B6C3F1 MICE OF EITHER SEX.

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TABLE 10 (cont'd)

NTP TOXICOLOGY AND CARCINOGENESIS STUDY RESULTS

NTP/TR REPORT CHEMICAL NAME CAS NUMBER	NO. — PEER REVIEW DATE	USE	ROUTE/DOSE	TESTING LABORATORY	NTP CHEMICAL MANAGER	RESULTS UNDER THE CONDITIONS OF THESE STUDIES
1,4-DICHLOROBENZENE 106-46-7	NTP-85-174 TR-319 03/26/86	SPACE DEODORANT; MOTH CONTROL; INTERMEDIATE IN ORGANIC SYNTHESES	GAVAGE (CORN OIL) RATS-- 0, 150 OR 300 MG/KG MICE— 0, 300 OR 600 MG/KG 5 DAYS/WEEK FOR 103 WEEKS	BATTELLE COLUMBUS LABORATORIES	DR. J. A. GOLDSTEIN	CLEAR EVIDENCE OF CARCINOGENICITY FOR MALE F344/N RATS, AS SHOWN BY AN INCREASED INCIDENCE OF RENAL TUBULAR CELL ADENOCARCINOMAS (1/50, 3/50, 7/50) AND FOR BOTH MALE AND FEMALE B6C3F1 MICE, AS SHOWN BY INCREASED INCIDENCE OF HEPATOCELLULAR CARCINOMAS (MALE: 14/50, 11/49, 32/50; FEMALE: 5/50, 5/48, 19/50) AND HEPATOCELLULAR ADENOMAS (MALE: 5/50, 12/49, 16/50; FEMALE: 10/50, 6/48, 21/50). NO EVIDENCE OF CARCINOGENICITY FOR FEMALE F344/N RATS. MARGINAL INCREASES WERE OBSERVED IN THE INCIDENCES OF PHEOCHROMOCYTOMAS OF THE ADRENAL GLAND IN MALE MICE(0/47,2/48,3/49). NONNEOPLASTIC EFFECTS IN THE KIDNEY OF MALE AND FEMALE RATS, IN THE LIVER OF MALE AND FEMALE MICE AND IN THE THYROID GLAND AND ADRENAL GLAND OF MALE MICE WERE ASSOCIATED WITH THE ADMINISTRATION OF 1,4-DICHLOROBENZENE.
DIMETHYL METHYLPHOSPHONATE 756-79-6	NTP-85-339 TR-323 08/19/86	VISCOSITY DEPRESSANT; FLAME RETARDANT; CHEMICAL INTERMEDIATE	GAVAGE: (CORN OIL)RATS—0,500, OR 1,000 MG/KG; MICE—0, 1000,OR 2,000 MG/KG 5 DAYS/WK, 103 WEEKS	LITTON BIONETICS, INC.	DR. J. K. DUNNICK	SOME EVIDENCE OF CARCINOGENIC ACTIVITY FOR MALE F344/N RATS AS SHOWN BY INCREASED INCIDENCE OF KIDNEY TUBULAR CELL HYPERPLASIA (0/50, 8/50, 9/49), TUBULAR CELL ADENOCARCINOMA (0/50, 2/50, 3/50), HYPERPLASIA OF TRANSITIONAL CELL EPITHELIUM (0/50, 23/50, 21/49). TRANSITIONAL CELL PAPILLOMA (0/50, 7/50, 3/49). NO EVIDENCE OF CARCINOGENIC ACTIVITY FOR FEMALE F344/N RATS. INADEQUATE STUDY OF CARCINOGENIC ACTIVITY IN MALE B6C3F1 MICE BECAUSE OF DECREASED SURVIVAL. NO EVIDENCE OF CARCINOGENIC ACTIVITY FOR FEMALE B6C3F1 MICE.
DIMETHYLVINYL CHLORIDE (1-CHLORO-2-METHYLPROPENE) 513-37-1	NTP-85-137 TR-316 P 12/09/85	IN ORGANIC SYNTHESES; FIRE HAZARD; AIR POLLUTANT	GAVAGE (CORN OIL) 0, 100 OR 200 MG/KG RATS—5 DAYS/WEEK FOR 103 WEEKS; MICE—5 DAYS/WEEK FOR 102 WEEKS	LITTON BIONETICS, INC.	DR. B. A. SCHWETZ	CLEAR EVIDENCE OF CARCINOGENICITY IN F344/N RATS AS INDICATED BY INCREASED INCIDENCE OF NASAL CAVITY EPITHELIAL CARCINOMA, SQUAMOUS CELL CARCINOMA OR ADENOCARCINOMA COMBINED (MALE: 0/47, 23/46, 28/32; FEMALE: 0/50, 16/49, 35/41), ORAL CAVITY SQUAMOUS CELL PAPILLOMA OR CARCINOMA COMBINED (MALE: 0/50, 5/50, 4/50; FEMALE: 0/50, 2/50, 5/50), ESOPHAGEAL EPITHELIAL HYPERPLASIA (MALE: 0/50, 6/50, 4/49; FEMALE: 0/49, 7/50, 4/49), SQUAMOUS CELL PAPILLOMAS OR CARCINOMAS (COMBINED) IN MALE RATS (0/50, 6/50, 4/49) AND EPITHELIAL HYPERPLASIA OF THE FORESTOMACH (MALE: 0/49, 24/50, 19/50; FEMALE: 0/50, 29/50, 24/49. CLEAR EVIDENCE OF CARCINOGENICITY IN B6C3F1 MICE AS SHOWN BY INCREASED INCIDENCE OF SQUAMOUS CELL NEOPLASMS OF THE FORESTOMACH (MALE:1/48,43/47,41/44; FEMALE: 0/50, 40/47. 38/43) AND SQUAMOUS CELL CARCINOMAS OF THE PREPUTIAL GLAND IN MALE MICE (1/48, 3/47, 16/44).

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TABLE 10 (cont'd)

NTP TOXICOLOGY AND CARCINOGENESIS STUDY RESULTS

NTP/TR REPORT CHEMICAL NAME CAS NUMBER	NO. — PEER REVIEW DATE	USE	ROUTE/DOSE	TESTING LABORATORY	NTP CHEMICAL MANAGER	RESULTS UNDER THE CONDITIONS OF THESE STUDIES
1,2-EPOXYBUTANE 106-88-7	NTP-86-071 TR-329 08/19/86	STABILIZER IN CHLORINATED HYDROCARBON SOLVENTS; CHEMICAL PRODUCTION	INHALATION: RATS-0,200, OR 400PPM (103WKS) MICE- 0, 50, OR 100PPM (102WKS) 6 HRS/DAY 5 DAYS/WEEK	BATTELLE PACIFIC NORTHWEST LABS	DR. J. K. DUNNICK	CLEAR EVIDENCE OF CARCINOGENIC ACTIVITY FOR MALE F344/N RATS AS SHOWN BY AN INCREASED INCIDENCE OF PAPILLARY ADENOMAS OF THE NASAL CAVITY (0/50, 0/50, 7/50) AND ALVEOLAR/BRONCHIOLAR ADENOMAS OR CARCINOMAS (COMBINED)(0/50, 2/50, 5/49). EQUIVOCAL EVIDENCE OF CARCINOGENIC ACTIVITY FOR FEMALE F344/N RATS AS SHOWN BY THE PRESENCE OF PAPILLARY ADENOMAS OF THE NASAL CAVITY IN TWO RATS IN THE 400-PPM GROUP (0/50, 0/50, 2/50). NO EVIDENCE OF CARCINOGENIC ACTIVITY FOR MALE OR FEMALE B6C3F1 MICE EXPOSED AT 50 OR 100 PPM. EXPOSURE WAS ASSOCIATED WITH NON-NEOPLASTIC LESIONS OF THE NASAL CAVITY IN RATS AND MICE.
ETHYLENE OXIDE 75-21-8	NTP-85-332 TR-326 08/19/86	CHEMICAL INTERMEDIATE, INSECT FUMGNT., STERILANT IN HOSPITALS	INHALATION: mice- 0, 50, or 100 ppm	BATTELLE PACIFIC NORTHWEST LABS	DR. T. R. LEWIS	CLEAR EVIDENCE OF CARCINOGENIC ACTIVITY FOR B6C3F1 MICE AS INDICATED BY INCREASED INCIDENCE OF ALVEOLAR/BRONCHIOLAR ADENOMA (MALE: 5/50, 11/50, 21/50; FEMALE: 2/49, 4/48, 17/49), ALVEOLAR/BRONCHIOLAR CARCINOMA (MALE:6/50,10/50,16/50; FEMALE: 0/49, 1/48, 7/49), HARDARIAN GLAND PAPILLARY CYSTADENOMA (MALE: 1/43, 9/44, 8/42; FEMALE: 1/46, 6/46, 0/47) AND IN FEMALE MICE UTERINE ADENOCARINOMA (0/49, 1/47, 5/49), MAMMARY GLAND ADENOCARCINOMA OR ADENOSQUAMOUS CARCINOMA (0/49, 8/49, 6/49) AND HEMATOPOIETIC SYSTEM (LYMPHOMA)(9/49, 6/48, 22/49).
METHYL CARBAMATE 598-55-0	NTP-86-008 TR-328 08/19/86	CHEMICAL INTERMEDIATE	GAVAGE: RATS- 0, 100 OR 200 MG/KG; MICE- 0, 500 OR 1,000 MG/KG	MICROBIOLOGICAL ASSOCIATES LABORATORIES	DR. P. C. CHAN	CLEAR EVIDENCE OF CARCINOGENIC ACTIVITY FOR F344/N RATS AS INDICATED BY INCREASED INCIDENCE OF HEPATOCELLULAR NEOPLASTIC NODULES (MALE: 3/50, 0/50, 3/49; FEMALE: 0/50,0/50, 5/49) AND HEPATOCELLULAR CARCINOMAS (MALE: 1/50, 0/50, 4/49; FEMALE: 0/50, 0/50, 2/50). THERE WAS NO EVIDENCE OF CARCINOGENIC ACTIVITY FOR B6C3F1 MICE OF EITHER SEX. THE TEST COMPOUND INDUCED RETINAL ATROPHY, CATARACTS, INFLAMMATION OF THE HARDEREAN GLAND IN F344/N RATS AND ADENOMATOUS HYPERPLASIA AND HISTIOCYTOSIS OF THE LUNG IN B6C3F1 MICE.
METHYL METHACRYLATE 80-62-6	NTP-85-106 TR-314 12/09/85	CHEMICAL INTERMEDIATE, DENTISTRY	INHALATION: RATS—MALE: 0, 500, OR 1,000 PPM; FEMALE: 0, 250, 500 PPM MICE—0, 500, OR 1,000 PPM; 6 HRS/D, 5 D/WK	BATTELLE PACIFIC NORTHWEST LABS	DR. P. C. CHAN	NO EVIDENCE OF CARCINOGENICITY IN F344/N RATS OR B6C3F1 MICE OF EITHER SEX.

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TABLE 10 (cont'd)

NTP TOXICOLOGY AND CARCINOGENESIS STUDY RESULTS

NTP/TR REPORT CHEMICAL NAME CAS NUMBER	NO. — PEER REVIEW DATE	USE	ROUTE/DOSE	TESTING LABORATORY	NTP CHEMICAL MANAGER	RESULTS UNDER THE CONDITIONS OF THESE STUDIES
OXYTETRACYCLINE HYDROCHLORIDE 2058-46-0	NTP-85-119 TR-315 12/09/85	ANTIBIOTIC	FEED: RATS: 0, 25,000, OR 50,000 PPM: MICE: 0, 6,300, 12,500 PPM 103 WEEKS	PHYSIOLOGICAL RESEARCH LABORATORIES	DR. K. M. ABDO	EQUIVOCAL EVIDENCE OF CARCINOGENICITY IN MALE F344/N RATS, AS INDICATED BY INCREASED INCIDENCES OF PHEOCHROMOCYTOMAS OF THE ADRENAL GLAND (10/50, 18/50, 24/50). EQUIVOCAL EVIDENCE OF CARCINOGENICITY IN FEMALE F344/N RATS, AS INDICATED BY INCREASED INCIDENCES OF NEOPLASMS OF THE PITUITARY GLAND (20/50, 24/50, 32/50). NO EVIDENCE OF CARCINOGENICITY IN MALE OR FEMALE B6C3F1 MICE.
PENTACHLORONITROBENZENE 82-68-8	NTP-85-227 TR-325 03/26/86	SOIL FUMIGANT	FEED: MICE - 0, 2,500, OR 5,000 PPM	EG&G MASON RESEARCH INSTITUTE	DR. J. K. DUNNICK	NO EVIDENCE OF CARCINOGENICITY FOR MALE OR FEMALE B6C3F1 MICE.
PHENYLEPHRINE HYDROCHLORIDE 61-76-7	NTP-85-215 TR-322 03/26/86	PHARMACEUTICAL	FEED: RATS— 0, 620, OR 1,250 PPM; MICE— 0, 1,250 OR 2,500 PPM FOR 103 WEEKS	PHYSIOLOGICAL RESEARCH LABORATORIES	DR. J. R. BUCHER	NO EVIDENCE OF CARCINOGENICITY FOR F344/N RATS OR B6C3F1 MICE OF EITHER SEX. SURVIVAL OF HIGH DOSE MALE RATS WAS GREATER THAN THAT OF CONTROLS, AND THE INCIDENCES OF MONONUCLEAR CELL LEUKEMIA (24/50, 9/50,5/50) AND PHEOCHROMOCYTOMAS (13/39,10/50,2/50) WERE LOWER IN DOSED THAN IN CONTROL MALE RATS.
ROTENONE 83-79-4	NTP-86-002 TR-320 08/19/86	PESTICIDE	FEED: RATS- 0, 38 OR 75 PPM; MICE- 0, 600 OR 1200 PPM	BATTELLE COLUMBUS LABORATORIES	DR. K. M. ABDO	THERE WAS EQUIVOCAL EVIDENCE OF CARCINOGENIC ACTIVITY IN MALE F344/N RATS AS INDICATED BY THE INCREASED INCIDENCE OF PARATHYROID GLAND ADENOMA (1/41, 0/44, 4/44). THERE WAS NO EVIDENCE OF CARCINOGENIC ACTIVITY FOR FEMALE F344/N RATS. THERE WAS NO EVIDENCE OF CARCINOGENIC ACTIVITY FOR B6C3F1 MICE OF EITHER SEX. THE DECREASED INCIDENCE OF LIVER NEOPLASMS IN MALE MICE MAY HAVE BEEN RELATED TO TEST CHEMICAL.
TETRAKIS(HYDROXY METHYL)PHOSPHONIUM CHLORIDE (THPC) 124-64-1	NTP-83-266 TR-296 03/26/86	FLAME RETARDANT	GAVAGE (WATER) RATS-0,3.75,OR 7.5 MG/KG;MICE-MALE: 0, 7.5 OR 15MG/KG;FEMALE: 0,15 OR 30MG/KG 5 DAYS/WEEK/ 103 WEEKS	BATTELLE COLUMBUS LABORATORIES	DR. C. W. JAMESON	NO EVIDENCE OF CARCINOGENICITY FOR F344/N RATS OR B6C3F1 MICE OF EITHER SEX.
TETRAKIS(HYDROXY METHYL)PHOSPHONIUM SULFATE (THPS) 55566-30-8	NTP-83-266 TR-296 03/26/86	FLAME RETARDANT	GAVAGE (WATER) (DEIONIZED WATER) 0, 5 OR 10 MG/KG RATS—5 DAYS/ WEEK/104 WEEKS MICE—5 DAYS/ WEEK/103 WEEKS	BATTELLE COLUMBUS LABORATORIES	DR. C. W. JAMESON	NO EVIDENCE OF CARCINOGENICITY FOR F344/N RATS OR B6C3F1 MICE OF EITHER SEX.

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TABLE 10 (cont'd)

NTP TOXICOLOGY AND CARCINOGENESIS STUDY RESULTS

NTP/TR REPORT CHEMICAL NAME CAS NUMBER	NO. — PEER REVIEW DATE	USE	ROUTE/DOSE	TESTING LABORATORY	NTP CHEMICAL MANAGER	RESULTS UNDER THE CONDITIONS OF THESE STUDIES
TRICHLOROETHYLENE 79-01-6	NTP-83-026 TR-273 08/19/86	INDUSTRIAL SOLVENT; EXTRACTANT FOR OLEORESINS AND CAFFEINE; ANESTHETIC	GAVAGE (CORN OIL) 0, 500 OR 1,000 MG/KG 5 DAYS/WEEK FOR 103 WEEKS	PAPANICOLAOU CANCER RESEARCH INSTITUTE	DR. J. H. MENNEAR	THESE STUDIES IN MALE AND FEMALE ACI, AUGUST, MARSHALL, AND OSBORNE-MENDEL RATS ARE CONSIDERED TO BE INADEQUATE FOR ASSESSING EITHER THE PRESENCE OR ABSENCE OF CARCINOGENIC ACTIVITY BECAUSE OF CHEMICALLY INDUCED TOXICITY, REDUCED SURVIVAL, AND DEFICIENCIES IN THE CONDUCT OF THE STUDIES AS REVEALED BY THE DATA AUDITS. THERE WERE INCREASED INCIDENCES OF RENAL TUBULAR CELL TUMORS OBSERVED IN EXPOSED RATS AND AN INCREASED INCIDENCE OF INTERSTITIAL CELL TUMORS OF THE TESTES IN EXPOSED MARSHALL RATS. FURTHER, THE ADMINISTRATION OF THE TEST CHEMICAL CAUSED RENAL TUBULAR CELL CYTOMEGALY (AIC-MALE: 0/49, 0/50, 40/49, 48/49; FEMALE: 0/49, 0/48, 43/47, 42/43, AUGUST-MALE: 0/50, 0/50, 46/50, 46/49; FEMALE: 0/50, 0/49, 46/48, 50/50, MARSHALL-MALE: 0/49, 0/49, 48/50, 47/47; FEMALE: 0/49, 0/50, 46/48, 43/44, OSBORNE-MENDEL-MALE: 0/50, 0/50, 48/50, 49/50; FEMALE: 0/50, 0/50, 48/50, 49/49).
XYLENES (MIXED) 1330-20-7	NTP-85-348 TR-327 03/26/86	SOLVENT; CLEANING AGENT; DEGREASER; CONSTITUENT OF FUELS	GAVAGE (CORN OIL): RATS- 0, 250 OR 500 MG/KG; MICE- 0, 500 OR 1,000 MG/KG 5 DAYS/WK FOR 103 WKS	BATTELLE COLUMBUS LABORATORIES	DR. W. C. EASTIN	NO EVIDENCE OF CARCINOGENICITY FOR F344/N RATS OR B6C3F1 MICE OF EITHER SEX.

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LEGENDS FOR TESTING TABLES
(Tables 11, 12, 13, 14, & 15)

CHEMICAL MANAGER CODES:

ABDK - Dr. K. Abdo NIEHS
ALLW - Dr. W. Allaben NCTR
BIRL - Dr. L. Birnbaum NIEHS
BISJ - Dr. J. Bishop NIEHS
BOOG - Dr. G. Boorman NIEHS
BRID - Dr. D. Bristol NIEHS
BUCJ - Dr. J. Bucher NIEHS
BURL - Dr. L. Burka NIEHS
CHAP - Dr. P. Chan NIEHS
CHHR - Dr. R. Chhabra NIEHS
COLJ - Dr. J. Collins NIEHS
CROG - Mr. G. Cronin NCTR
DIEM - Dr. M. Dieter NIEHS
DUNJ - Dr. J. Dunnick NIEHS
EASW - Dr. W. Eastin NIEHS
FOWB - Dr. B. Fowler NIEHS
FREJ - Dr. J. French NIEHS
GRED - Dr. D. Greenman NCTR
HEAH - Dr. H. Hearn FCRC
HINJ - Dr. J. Hinson NCTR
HUFJ - Dr. J. Huff NIEHS
IRWR - Dr. R. Irwin NIEHS
JACC - Dr. C. Jackson NCTR
JAMW - Dr. W. Jameson NIEHS
KADF - Dr. F. Kadlubar NCTR
KARF - Dr. F. Kari NIEHS
LALJ - Dr. J. Lal NIOSH
LEWT - Dr. T. Lewis NIOSH
LITN - Dr. N. Littlefield NCTR
LOWL - Dr. L. Lowry NIOSH
LUSM - Dr. M. Luster NIEHS
MARR - Dr. R. Maronpot NIEHS
MATH - Dr. H. Matthews NIEHS
MCCE - Dr. E. McConnell NIEHS
MELR - Dr. R. Melnick NIEHS
MENJ - Dr. J. Mennear NIEHS
MOOW - Mr. W. Moorman NIOSH
NOCM - No Chemical Manager
RAOG - Dr. G. Rao NIEHS
RAUE - Dr. E. Rauckman NIEHS
ROYJ - Dr. J. Roycroft NIEHS
SCHB - Dr. B. Schwetz NIEHS
SPAJ - Dr. J. Spalding NIEHS
STAS - Mr. S. Stasiewicz NIEHS
STES - Dr. S. Stefanski NIEHS
THOM - Dr. M. Thompson NIEHS
URAL - Dr. L. Uraih NIEHS
WALD - Dr. D. Walters NIEHS
WHIC - Dr. C. Whitmire NIEHS
WOLG - Dr. G. Wolff NCTR
YANR - Dr. R. Yang NIEHS

ROUTE - ROUTE OF ADMINISTRATION:

FEED - Oral in Feed
GAV - Oral, Gavage
INHAL - Inhalation
IP/IJ - Intraperitoneal Injection
SP - Skin Paint
WATER - Oral with Water

SPECIES:

M - MICE
H - HAMSTERS
R - RATS
GP - GUINEA PIGS

TABLE 11

CHEMICALS IN PRECHRONIC PHASE OF TOXICOLOGY AND CARCINOGENESIS STUDIES AT THE END OF FY 1986

SEQ NO.	CHEMICAL NAME	PRIMARY CAS NUMBER	SPECIES	ROUTE	CHEM MGR
1	ACETONE	67-64-1	RM	WATER	RAUE
2	ACETONITRILE	75-05-8	RM	INHAL	ROYJ
3	2-(4-AMINOPHENYL)-6-METHYL-7-BENZOTHIAZO	130-17-6	RM	FEED	RAUE
4	AZODICARBONAMIDE	123-77-3	RM	INHAL	BIRL
5	BENZONITRILE	100-47-0	RM	GAV	IRWR
6	2,2-BIS(BROMOMETHYL)-1,3-PROPANEDIOL	3296-90-0	RM	FEED	DUNJ
7	TERT-BUTYL ALCOHOL	75-65-0	RM	INHAL	MARR
8	TERT-BUTYL PERBENZOATE	614-45-9	RM	ORAL	MATH
9	BUTYRALDEHYDE	123-72-8	RM	INHAL	FREJ
10	CHLOROPRENE	126-99-8	RM	INHAL	MELP
11	2-CHLORO-1-PROPANOL + 1-CHLORO-2-PROPANO	127-00-4	RM	WATER	YANR
12	1,8-CINEOL	470-82-6	RM	FEED	WOLG
13	1,8-CINEOL	470-82-6	RM	GAV	WOLG
14	CINNAMALDEHYDE	104-55-2	RM	FEED	WOLG
15	COBALT SULFATE HEPTAHYDRATE	10026-24-1	RM	INHAL	BUCJ
16	D & C YELLOW NO. 11	8003-22-3	RM	FEED	EASW
17	5,6-DICHLORO-2-BENZOTHIAZOLAMINE	24072-75-1	RM	FEED	RAUE
18	1,2-DICHLOROETHANE	107-06-2	R	GAV	RAUE
19	1,2-DICHLOROETHANE	107-06-2	RM	WATER	RAUE
20	1,2-DICHLOROETHANE	107-06-2	R	WATER	RAUE

TABLE 11

CHEMICALS IN PRECHRONIC PHASE OF TOXICOLOGY AND CARCINOGENESIS STUDIES AT THE END OF FY 1986

SEQ NO.	CHEMICAL NAME	PRIMARY CAS NUMBER	SPECIES	ROUTE	CHEM MGR
21	1,2-DICHLOROETHANE	107-06-2	R	WATER	RAUE
22	1,2-DIHYDRO-2,2,4-TRIMETHYLQUINOLINE (MO	147-47-7	RM	SP	FREJ
23	1,2-DIHYDRO-2,2,4-TRIMETHYLQUINOLINE (PO	26780-96-1	RM	SP	FREJ
24	1,6-HEXANEDIAMINE, DIHYDROCHLORIDE	6055-52-3	RM	INHAL	FREJ
25	2-HYDROXY-4-METHOXYBENZOPHENONE	131-57-7	RM	FEED	FREJ
26	2-HYDROXY-4-METHOXYBENZOPHENONE	131-57-7	RM	SP	FREJ
27	6-METHOXY-2-BENZOTHIAZOLAMINE	1747-60-0	RM	FEED	RAUE
28	4-(6-METHYL-2-BENZOTHIAZOLYL)-BENZENAMIN	92-36-4	RM	FEED	RAUE
29	METHYL BROMIDE	74-83-9	RM	INHAL	YANR
30	3-METHYL-6-METHOXY-2-AMINO-BENZOTHIAZOLI	NOCAS0884	RM	FEED	RAUE
31	NICKEL (II) OXIDE	1313-99-1	RM	INHAL	DUNJ
32	NICKEL SULFATE HEXAHYDRATE	10101-97-0	RM	INHAL	DUNJ
33	M-NITROBENZOIC ACID	121-92-6	RM	FEED	ABDK
34	P-NITROBENZOIC ACID	62-23-7	RM	FEED	ABDK
35	PENTACHLOROBENZENE	608-93-5	RM	FEED	YANR
36	SALICYLAZOSULFAPYRIDINE	599-79-1	RM	GAV	KARF
37	SCOPOLAMINE HYDROBROMIDE	114-49-8	RM	GAV	RAUE
38	TETRACHLOROPHTHALIC ANHYDRIDE	117-08-8	RM	GAV	KARF
39	TETRAFLUOROETHYLENE	116-14-3	RM	INHAL	ROYJ
40	THEOPHYLLINE	58-55-9	RM	GAV	COLJ

TABLE 11

CHEMICALS IN PRECHRONIC PHASE OF TOXICOLOGY AND CARCINOGENESIS STUDIES AT THE END OF FY 1986

SEQ NO.	CHEMICAL NAME	PRIMARY CAS NUMBER	SPECIES	ROUTE	CHEM MGR
41	THEOPHYLLINE	58-55-9	RM	FEED	COLJ
42	TRICHLORFON	52-68-6	RM	FEED	CHAP
43	TRIETHANOLAMINE	102-71-6	RM	SP	MELR

TABLE 12

CHEMICALS IN THE CHRONIC PHASE OF TOXICOLOGY AND CARCINOGENESIS STUDIES AT THE END OF FY 1986

SEQ NO.	CHEMICAL NAME	PRIMARY CAS NUMBER	SPECIES	ROUTE	CHEM MGR
1	ACETAMINOPHEN	103-90-2	RM	FEED	IRWR
2	ALLYL GLYCIDYL ETHER	106-92-3	RM	INHAL	BOOG
3	1-AMINO-2,4-DIBROMOANTHRAQUINONE	81-49-2	RM	FEED	HUFJ
4	2-AMINO-4-NITROPHENOL	99-57-0	RM	GAV	IRWR
5	2-AMINO-5-NITROPHENOL	121-88-0	RM	GAV	IRWR
6	AMPHETAMINE SULFATE	60-13-9	RM	FEED	DUNJ
7	BARIUM CHLORIDE DIHYDRATE	10326-27-9	RM	WATER	GUPB
8	BENZALDEHYDE	100-52-7	RM	GAV	BISJ
9	BENZOFURAN	271-89-6	RM	GAV	IRWR
10	BENZYL ACETATE	140-11-4	RM	FEED	ABDK
11	BENZYL ALCOHOL	100-51-6	RM	GAV	DIEM
12	O-BENZYL-P-CHLOROPHENOL	120-32-1	M	SP	BIRL
13	O-BENZYL-P-CHLOROPHENOL	120-32-1	RM	GAV	BIRL
14	BROMOFORM	75-25-2	RM	GAV	MELR
15	1,3-BUTADIENE	106-99-0	M	INHAL	MELR
16	TERT-BUTYL ALCOHOL	75-65-0	RM	WATER	MARR
17	GAMMA-BUTYROLACTONE	96-48-0	RM	GAV	IRWR
18	D-CARVONE	2244-16-8	RM	GAV	ROYJ
19	CASTOR OIL	8001-79-4	RM	FEED	COLJ
20	CHLORAMINE	10599-90-3	RM	WATER	WHIC

TABLE 12

CHEMICALS IN THE CHRONIC PHASE OF TOXICOLOGY AND CARCINOGENESIS STUDIES AT THE END OF FY 1986

SEQ NO.	CHEMICAL NAME	PRIMARY CAS NUMBER	SPECIES	ROUTE	CHEM MGR
21	CHLORAMINE	10599-90-3	RM	WATER	WHIC
22	CHLOROACETOPHENONE (CN)	532-27-4	RM	INHAL	MELR
23	P-CHLOROANILINE	106-47-8	RM	GAV	CHHR
24	O-CHLOROBENZALMALONONITRILE (CS)	2698-41-1	RM	INHAL	ABDK
25	C.I. ACID ORANGE 3	6373-74-6	RM	GAV	MENJ
26	C.I. ACID RED 114	6459-94-5	R	WATER	MENJ
27	C.I. DIRECT BLUE 15	2429-74-5	R	WATER	MENJ
28	C.I. DIRECT BLUE 218	28407-37-6	RM	FEED	MENJ
29	C.I. PIGMENT RED 3	2425-85-6	RM	FEED	MENJ
30	C.I. PIGMENT RED 23	6471-49-4	RM	FEED	MENJ
31	COCONUT DIETHANOLAMIDE	68603-42-9	RM	SP	EASW
32	CORN OIL	8001-30-7	R	GAV	BOOG
33	COUMARIN	91-64-5	RM	GAV	THOM
34	2,4-DIAMINOPHENOL DIHYDROCHLORIDE	137-09-7	RM	GAV	IRWR
35	4,4'-DIAMINO-2,2'-STILBENEDISULFONIC ACI	81-11-8	RM	FEED	EASW
36	2,3-DIBROMO-1-PROPANOL	96-13-9	RM	SP	MELR
37	DICHLOROMETHANE (METHYLENE CHLORIDE)	75-09-2	R	GAV	BOOG
38	2,4-DICHLOROPHENOL	120-83-2	RM	FEED	MELR
39	DICHLORVOS	62-73-7	RM	GAV	CHAP
40	DIETHANOLAMINE	111-42-2	RM	GAV	MELR

TABLE 12

CHEMICALS IN THE CHRONIC PHASE OF TOXICOLOGY AND CARCINOGENESIS STUDIES AT THE END OF FY 1986

SEQ NO.	CHEMICAL NAME	PRIMARY CAS NUMBER	SPECIES	ROUTE	CHEM MGR
41	DIETHYL PHTHALATE	84-66-2	RM	SP	RAUE
42	DIETHYL PHTHALATE	84-66-2	M	SP	RAUE
43	3,4-DIHYDROCOUMARIN	119-84-6	RM	GAV	THOM
44	DIMETHOXANE	828-00-2	RM	GAV	ABDK
45	3,3'-DIMETHOXYBENZIDINE	119-90-4	R	WATER	MENJ
46	N,N-DIMETHYLANILINE	121-69-7	RM	GAV	ABDK
47	3,3'-DIMETHYLBENZIDINE	119-93-7	R	WATER	MENJ
48	DIMETHYL PHTHALATE	131-11-3	M	SP	RAUE
49	DIPHENHYDRAMINE HYDROCHLORIDE	147-24-0	RM	FEED	MELR
50	DIPHENYLHYDANTOIN (PHENYTOIN)	57-41-0	RM	FEED	CHHR
51	DMBA(DIMETHYLBENZANTHRACENE)/TPA(TETRADE	57-97-6	R	SP	EASW
52	DMBA(DIMETHYLBENZANTHRACENE)/TPA(TETRADE	57-97-6	M	SP	EASW
53	DOXYLAMINE	469-21-6	RM	FEED	JACC
54	EPINEPHRINE HYDROCHLORIDE	55-31-2	RM	INHAL	ROYJ
55	1,2-EPOXYHEXADECANE	7320-37-8	RM	SP	KARF
56	ERYTHROMYCIN STEARATE	643-22-1	RM	FEED	FREJ
57	ETHYL BROMIDE	74-96-4	RM	INHAL	ROYJ
58	ETHYL CHLORIDE	75-00-3	RM	INHAL	ROYJ
59	ETHYLENE GLYCOL	107-21-1	M	FEED	MELR
60	ETHYLENE GLYCOL MONOETHYL ETHER (EGMEE)	110-80-5	RM	GAV	LALJ

TABLE 12

CHEMICALS IN THE CHRONIC PHASE OF TOXICOLOGY AND CARCINOGENESIS STUDIES AT THE END OF FY 1986

SEQ NO.	CHEMICAL NAME	PRIMARY CAS NUMBER	SPECIES	ROUTE	CHEM MGR
61	ETHYLENE THIOUREA	96-45-7	RM	FEED	CHHR
62	FURAN	110-00-9	RM	GAV	IRWR
63	FURFURAL	98-01-1	RM	GAV	IRWR
64	FUROSEMIDE	54-31-9	RM	FEED	BUCJ
65	GLUTARALDEHYDE	111-30-8	RM	SP	KARF
66	GLYCIDOL	556-52-5	RM	GAV	IRWR
67	HC YELLOW 4	52551-67-4	RM	FEED	EASW
68	HEXACHLOROCYCLOPENTADIENE	77-47-4	RM	INHAL	ABDK
69	HEXACHLOROETHANE	67-72-1	R	GAV	EASW
70	HEXAMETHYL-P-ROSANILINE CHLORIDE	548-62-9	RM	FEED	LITN
71	HEXYLRESORCINOL	136-77-6	RM	GAV	CHHR
72	HYDROCHLOROTHIAZIDE	58-93-5	RM	FEED	BUCJ
73	HYDROQUINONE	123-31-9	RM	GAV	BRID
74	INIT/PROM COMPARATIVE MOUSE STUDY (DMBA/	57-97-6	MM	SP	EASW
75	INIT/PROM COMPARATIVE MOUSE STUDY (DMBA/	57-97-6	MM	SP	EASW
76	INIT/PROM COMPARATIVE MOUSE STUDY (DMBA/	57-97-6	MM	SP	EASW
77	IODINATED GLYCEROL	5634-39-9	RM	GAV	FREJ
78	LAURIC ACID DIETHANOLAMINE CONDENSATE	120-40-1	RM	SP	EASW
79	D-LIMONENE	5989-27-5	RM	GAV	JAMW
80	MALONALDEHYDE, SODIUM SALT	24382-04-5	RM	GAV	SPAJ

TABLE 12

CHEMICALS IN THE CHRONIC PHASE OF TOXICOLOGY AND CARCINOGENESIS STUDIES AT THE END OF FY 1986

SEQ NO.	CHEMICAL NAME	PRIMARY CAS NUMBER	SPECIES	ROUTE	CHEM MGR
81	MANGANESE SULFATE MONOHYDRATE	10034-96-5	RM	FEED	WALD
82	MERCAPTOBENZOTHIAZOLE	149-30-4	RM	GAV	DIEM
83	MERCURIC CHLORIDE	7487-94-7	RM	GAV	DIEM
84	8-METHOXYPSORALEN	298-81-7	R	GAV	DUNJ
85	ALPHA-METHYLBENZYL ALCOHOL	98-85-1	RM	GAV	DIEM
86	METHYL BROMIDE	74-83-9	M	INHAL	YANR
87	METHYLDOPA	555-30-6	RM	FEED	DUNJ
88	METHYL ETHYL KETONE PEROXIDE	1338-23-4	RM	SP	ABOK
89	N-METHYLOLACRYLAMIDE	924-42-5	RM	GAV	BUCJ
90	METHYLPHENIDATE HYDROCHLORIDE	298-59-9	RM	FEED	RAUE
91	MIREX	2385-85-5	R	FEED	HUFJ
92	MIREX	2385-85-5	R	FEED	HUFJ
93	MONOCHLOROACETIC ACID	79-11-8	RM	GAV	EASW
94	MOUSE AGING STUDY		M		RAOG
95	NALIDIXIC ACID	389-08-2	RM	FEED	FREJ
96	NAPHTHALENE	91-20-3	M	INHAL	URAL
97	P-NITROANILINE	100-01-6	M	GAV	CHHR
98	O-NITROANISOLE	91-23-6	RM	FEED	CHHR
99	NITROFURANTOIN	67-20-9	RM	FEED	FREJ
100	NITROFURAZONE	59-87-0	RM	FEED	KARF

TABLE 12

CHEMICALS IN THE CHRONIC PHASE OF TOXICOLOGY AND CARCINOGENESIS STUDIES AT THE END OF FY 1986

SEQ NO.	CHEMICAL NAME	PRIMARY CAS NUMBER	SPECIES	ROUTE	CHEM MGR
101	P-NITROPHENOL	100-02-7	M	SP	IRWR
102	P-NITROPHENOL	100-02-7	M	SP	IRWR
103	OCHRATOXIN A	303-47-9	R	GAV	BOOG
104	OLEIC ACID DIETHANOLAMINE	13961-86-9	RM	SP	EASW
105	PENICILLIN VK	132-98-9	RM	GAV	DUNJ
106	PENTACHLOROANISOLE	1825-21-4	RM	GAV	BRID
107	PENTACHLOROPHENOL, DOWICIDE EC-7	87-86-5	M	FEED	MCCE
108	PENTACHLOROPHENOL, TECHNICAL	87-86-5	M	FEED	MCCE
109	PENTAERYTHRITOL TETRANITRATE	78-11-5	RM	FEED	BUCJ
110	PHENYLBUTAZONE	50-33-9	RM	GAV	KARF
111	N-PHENYL-2-NAPHTHYLAMINE	135-88-6	RM	FEED	ABDK
112	POLYBROMINATED BIPHENYL MIXTURE (FIREMAS	67774-32-7	RM	FEED	CHHR
113	POLYSORBATE 80 (GLYCOL)	9005-65-6	RM	FEED	ABDK
114	PROBENECID	57-66-9	RM	GAV	STES
115	PROMETHAZINE HYDROCHLORIDE	58-33-3	RM	GAV	LUSM
116	PYRIDINE	110-86-1	RM	GAV	FREJ
117	PYRILAMINE	91-84-9	RM	FEED	ALLW
118	QUERCETIN	117-39-5	R	FEED	DUNJ
119	RESORCINOL	108-46-3	RM	GAV	IRWR
120	RESORCINOL	108-46-3	R	GAV	IRWR

TABLE 12

CHEMICALS IN THE CHRONIC PHASE OF TOXICOLOGY AND CARCINOGENESIS STUDIES AT THE END OF FY 1986

SEQ NO.	CHEMICAL NAME	PRIMARY CAS NUMBER	SPECIES	ROUTE	CHEM MGR
121	RHODAMINE 6G	989-38-8	RM	FEED	FREJ
122	ROTENONE	83-79-4	R	IP/IJ	ALLW
123	ROXARSONE	121-19-7	RM	FEED	ABDK
124	SAFFLOWER OIL	8001-23-8	R	GAV	BOOG
125	SODIUM AZIDE	26628-22-8	R	GAV	ABDK
126	SODIUM DODECYL SULFATE	151-21-3	RM	FEED	IRWR
127	SODIUM FLUORIDE	7681-49-4	RM	WATER	BUCJ
128	SODIUM XYLENESULFONATE	1300-72-7	RM	FEED	IRWR
129	SUCCINIC ANHYDRIDE	108-30-5	M	GAV	MELR
130	SUCCINIC ANHYDRIDE	108-30-5	R	GAV	MELR
131	SULFAMETHAZINE	57-68-1	RM	FEED	LITN
132	TALC	14807-96-6	RM	INHAL	DIEM
133	TETRACHLOROETHYLENE	127-18-4	R	GAV	MENJ
134	TETRACHLOROETHYLENE	127-18-4	R	GAV	MENJ
135	TETRACHLOROETHYLENE	127-18-4	R	GAV	MENJ
136	TETRACHLOROETHYLENE	127-18-4	R	GAV	MENJ
137	TETRACHLOROETHYLENE	127-18-4	M	GAV	MENJ
138	TETRACYCLINE HYDROCHLORIDE	64-75-5	RM	FEED	ABDK
139	TETRANITROMETHANE	509-14-8	RM	INHAL	BUCJ
140	TITANOCENE DICHLORIDE	1271-19-8	R	GAV	DIEM

TABLE 12

CHEMICALS IN THE CHRONIC PHASE OF TOXICOLOGY AND CARCINOGENESIS STUDIES AT THE END OF FY 1986

SEQ NO.	CHEMICAL NAME	PRIMARY CAS NUMBER	SPECIES	ROUTE	CHEM MGR
141	TOLUENE (NITRATION GRADE)	108-88-3	RM	INHAL	HUFJ
142	TRIAMTERENE	396-01-0	RM	FEED	WHIC
143	TRICAPRYLIN	538-23-8	R	GAV	BOOG
144	TRICHLORFON	52-68-6	RM	GAV	CHAP
145	1,1,1-TRICHLOROETHANE (METHYL CHLOROFORM	71-55-6	RM	GAV	BIRL
146	1,2,3-TRICHLOROPROPANE	96-18-4	RM	GAV	BURL
147	TRICRESYL PHOSPHATE	1330-78-5	RM	FEED	IRWR
148	TRIPELENNAMINE HYDROCHLORIDE	154-69-8	RM	FEED	JACC
149	TRIPROLIDINE	486-12-4	RM	FEED	ALLW
150	TRIS(2-CHLOROETHYL) PHOSPHATE	115-96-8	RM	GAV	MATH
151	TURMERIC, OLEORESIN (CURCUMIN)	8024-37-1	RM	FEED	FREJ
152	VINYL CYCLOHEXENE DIEPOXIDE	106-87-6	RM	SP	CHHR
153	VINYL TOLUENE	25013-15-4	RM	INHAL	BOOG
154	WOLLASTONITE CALCIUM SILICATES	13983-17-0	R	INHAL	MCCE

TABLE 13

CHEMICALS SCHEDULED TO START IN THE PRECHRONIC PHASE OF TOXICOLOGY AND CARCINOGENESIS STUDIES IN FY 1987*

SEQ NO.	CHEMICAL NAME	PRIMARY CAS NUMBER	SPECIES	ROUTE	CHEM MGR
1	ANTIMONY POTASSIUM TARTRATE	28300-74-5	RM	IP/IJ	DIEM
2	ANTIMONY POTASSIUM TARTRATE	28300-74-5	RM	WATER	DIEM
3	CARISOPRODOL	78-44-4	RM	GAV	CHAP
4	CHEMICAL MIXTURE - DRINKING WATER	CHEMMIXH2O			YANR
5	1-CHLORO-2-PROPANOL	127-00-4	RM	INHAL	YANR
6	2-CHLORO-1-PROPANOL + 1-CHLORO-2-PROPANO	127-00-4	RM	INHAL	YANR
7	M-CRESOL	108-39-4	RM	FEED	RAUE
8	CRESOL (MIXED ISOMERS)	1319-77-3	RM	FEED	RAUE
9	O-CRESOL	95-48-7	RM	FEED	RAUE
10	P-CRESOL	106-44-5	RM	FEED	RAUE
11	CUPRIC SULFATE	7758-99-8	RM	WATER	RAUE
12	DIBUTYL PHTHALATE	84-74-2	RM	FEED	RAUE
13	DIETHANOLAMINE	111-42-2	RM	SP	MELR
14	DIETHANOLAMINE	111-42-2	RM	WATER	MELR
15	DIMETHYLFORMAMIDE	68-12-2	RM	INHAL	LEWT
16	FERROCENE	102-54-5	RM	GAV	DIEM
17	FORMIC ACID	64-18-6	RM	INHAL	ABDK
18	GLUTARALDEHYDE	111-30-8	RM	INHAL	HARF
19	ISOBUTYL NITRITE	542-56-3		INHAL	JACC
20	ISOPRENE	78-79-5	RM	INHAL	MELR

* Known chemicals as of 10/01/86. Others may be scheduled as protocols are finalized

TABLE 13 (Cont.)

CHEMICALS SCHEDULED TO START IN THE PRECHRONIC PHASE OF TOXICOLOGY AND CARCINOGENESIS STUDIES IN FY 1987*

SEQ NO.	CHEMICAL NAME	PRIMARY CAS NUMBER	SPECIES	ROUTE	CHEM MGR
21	2-MERCAPTOBENZIMIDAZOLE	583-39-1	RM	INHAL	COLJ
22	METHYL ETHYL KETONE PEROXIDE	1338-23-4	RM	SP	ABDK
23	METHYLEUGENOL	93-15-2	RM	FEED	BRID
24	NITROMETHANE	75-52-5	RM	INHAL	ROYJ
25	PHENOLPHTHALEIN	77-09-8	RM	FEED	HALL
26	RIDDELLINE	23246-96-0	RM	GAV	CHAP
27	SODIUM CYANIDE	143-33-9	RM	WATER	RAUE
28	SODIUM SELENATE	13410-01-0	RM	WATER	RAUE
29	SODIUM SELENITE	10102-18-8	RM	WATER	RAUE
30	SODIUM XYLENESULFONATE	1300-72-7		FEED	IRWR
31	1,2,4,5-TETRACHLOROBENZENE	95-94-3	RM	FEED	YANR
32	TETRACHLOROPHTHALIC ANHYDRIDE	117-08-8	RM	GAV	KARF
33	THIOPHENE	110-02-1	RM	INHAL	IRWR

* Known chemicals as of 10/01/86. Others may be scheduled as protocols are finalized

TABLE 14

CHEMICALS SCHEDULED TO START IN THE CHRONIC PHASE OF TOXICOLOGY AND CARCINOGENESIS STUDIES IN FY 1987*

SEQ NO.	CHEMICAL NAME	PRIMARY CAS NUMBER	SPECIES	ROUTE	CHEM MGR
1	ACETONITRILE	75-05-8	RM	INHAL	ROYJ
2	BENZETHONIUM CHLORIDE	121-54-0	RM	SP	EASW
3	TERT-BUTYL ALCOHOL	75-65-0	RM	WATER	MARR
4	CODEINE	76-57-3	RM	GAV	DUNJ
5	CORN OIL	8001-30-7	R	GAV	BOOG
6	DICHLOROMETHAN (METHYLENE CHLORIDE)	75-09-2	R	GAV	BOOG
7	MOLYBDENUM TRIOXIDE	1313-27-5	RM	INHAL	CHAP
8	NICKEL SULFATE HEXAHYDRATE	10101-97-0	RM	INHAL	DUNJ
9	NICKEL SUBSULFIDE	12035-72-2	RM	INHAL	DUNJ
10	SAFFLOWER OIL	8001-23-8	R	GAV	BOOG
11	4,4'-THIOBIS(6-TERT-BUTYL-M-CRESOL)	96-69-5	RM	FEED	BIRL
12	TRICAPRYLIN	538-23-8	R	GAV	BOOG

* Known chemicals as of 10/01/86. Others may be scheduled as protocols are finalized

TABLE 15

CHEMICALS FOR WHICH TOXICOLOGY AND CARCINOGENESIS STUDIES WILL BE COMPLETED IN FY 1987

SEQ NO.	CHEMICAL NAME	PRIMARY CAS NUMBER	SPECIES	ROUTE	CHEM MGR
1	2-AMINO-4-NITROPHENOL	99-57-0	RM	GAV	IRWR
2	2-AMINO-5-NITROPHENOL	121-88-0	RM	GAV	IRWR
3	BENZYL ALCOHOL	100-51-6	RM	GAV	DIEM
4	BROMOFORM	75-25-2	RM	GAV	MELR
5	P-CHLOROANILINE	106-47-8	RM	GAV	CHHR
6	C.I. ACID ORANGE 3	6373-74-6	RM	GAV	MENJ
7	2,4-DICHLOROPHENOL	120-83-2	RM	FEED	MELR
8	DICHLORVOS	62-73-7	RM	GAV	CHAP
9	ERYTHROMYCIN STEARATE	643-22-1	RM	FEED	FREJ
10	ETHYL CHLORIDE	75-00-3	RM	INHAL	ROYJ
11	HEXYLRESORCINOL	136-77-6	RM	GAV	CHHR
12	IODINATED GLYCEROL	5634-39-9	RM	GAV	FREJ
13	D-LIMONENE	5989-27-5	RM	GAV	JAMW
14	MALONALDEHYDE, SODIUM SALT	24382-04-5	RM	GAV	SPAJ
15	MERCAPTOBENZOTHIAZOLE	149-30-4	RM	GAV	DIEM
16	METHYLDOPA	555-30-6	RM	FEED	DUNJ
17	N-METHYLOLACRYLAMIDE	924-42-5	RM	GAV	BUCJ
18	MIREX	2385-85-5	R	FEED	HUFJ
19	MIREX	2385-85-5	R	FEED	HUFJ
20	NITROFURANTOIN	67-20-9	RM	FEED	FREJ

TABLE 15

CHEMICALS FOR WHICH TOXICOLOGY AND CARCINOGENESIS STUDIES WILL BE COMPLETED IN FY 1987

SEQ NO.	CHEMICAL NAME	PRIMARY CAS NUMBER	SPECIES	ROUTE	CHEM MGR
21	NITROFURAZONE	59-87-0	RM	FEED	KARF
22	PENICILLIN VK	132-98-9	RM	GAV	DUNJ
23	PENTACHLOROPHENOL, DOWICIDE EC-7	87-86-5	M	FEED	MCCE
24	PENTACHLOROPHENOL, TECHNICAL	87-86-5	M	FEED	MCCE
25	N-PHENYL-2-NAPHTHYLAMINE	135-88-6	RM	FEED	ABDK
26	ROXARSONE	121-19-7	RM	FEED	ABDK
27	TETRACYCLINE HYDROCHLORIDE	64-75-5	RM	FEED	ABDK

NCTR

TESTING - PRECHRONIC AND TWO-YEAR STUDIES

This program conducts toxicological evaluations on food additives, animal or human drugs, pesticides, or other chemicals of interest to FDA nominated to the NTP. In addition to testing, this program also attempts to determine structure/activity relationships between toxicological endpoints of structurally similar compounds and develops better methods for determining toxicity of chemicals. The NCTR initiated studies examining the structure/activity relationship of five antihistamines, namely: doxylamine, tripelennamine, triprolidine, pyrilamine, and methapyrilene.

FY 1986 ACCOMPLISHMENTS

The chronic testing phase for two antihistamines, triprolidine and methapyrilene (mice only), was begun in FY 1986. Protocols were also prepared to test the effects of the above five antihistamines on sperm morphology and vaginal cytology. However, because of Gramm-Rudman-Hollings budgetary constraints experienced in FY 1986, the chronic studies for tripelennamine and methapyrilene were terminated and the sperm morphology/vaginal cytology studies were not initiated.

Twenty-eight day repeated dose studies were completed with the compound 1,8-cineole. These studies compared microencapsulated 1,8-cineole in the feed against orally gavaged 1,8-cineole in both $B6C3F_1$ male and female mice and Fischer 344 male and female rats. A final report for this study was submitted. Methods development continues for a technique to microencapsulate the food flavoring cinnamaldehyde.

Executive summaries for 2,4-dinitroaniline, 1,3-dichloro-5,5'-dimethylhydantoin, N-isopropyl-N'-phenyl-p-phenylenediamine, and trimellitic anhydride were prepared for review by the TDC. The studies and status of each study are summarized below.

Pyrilamine

Two-Year Chronic Studies -- Dose levels for the two-year chronic bioassay were: rats - 0, 300, 1500, and 3000 parts per million (ppm); mice - 0, 150, 750, and 1500 ppm (all calculated as the free amine). The bioassays began in February 1985. Interim 15-month sacrifices were conducted in April/May 1986. (CONTACT PERSON: Dr. W.T. Allaben)

Methapyrilene

Two-Year Chronic Study -- Based on budget restrictions, the chronic study phase of testing methapyrilene in $B6C3F_1$ mice was given a low priority and terminated one month after the study was initiated. No clinical or histopathology data were collected.

Doxylamine

Two-Year Chronic Study -- The chronic phase of testing doxylamine in Fischer 344 rats and B6C3F_1 mice was completed in April and May, 1986. Dose levels of 0, 500, 1000, and 2000 ppm (rats) and 0, 190, 375, and 750 ppm (mice) were administered in the feed for 24 months. Necropsy and histopathology examinations were performed on the 65-week sacrifice animals and an interim report will be available the last quarter of FY 1986. However, due to budget restrictions, complete necropsies only (no histopathology examinations) were performed on the 24-month, terminal sacrificed animals. The tissues were, however, stored in formalin. An interim report of the necropsy findings will be available the first quarter of FY 1987. (CONTACT PERSON: Dr. C.D. Jackson)

Tripelennamine

Two-Year Chronic Study -- Due to budget restrictions, the chronic phase of testing tripelennamine in Fischer 344 rats and B6C3F_1 mice was terminated in May 1986. Dose levels of 0, 100, 200, and 400 ppm (rats) and 0, 500, 1000, and 2000 ppm (mice) had been administered for approximately 11 months when the study was terminated. Necropsies were performed on animals in the controls, low dose and high dose groups and the tissues were stored in formalin. All other animals were destroyed. No histopathology examinations were performed. An interim report on the necropsy findings will be available the first quarter of FY 1987. (CONTACT PERSON: Dr. C.D. Jackson)

Triprolidine

Two-Year Chronic Study -- Dose levels for the chronic bioassay were: rats - 0, 500, 1000, and 2000 ppm; mice - 0, 500, 1000, and 2000 ppm (as the free amine). The study began in July 1985. An interim 15-month sacrifice was performed in October/November, 1986. (CONTACT PERSON: Dr. W.T. Allaben)

Caffeine

Two-Year Chronic Study -- The food additive caffeine will not be tested in chronic studies because of the lack of evidence of toxicity or preneoplastic lesions in 90-day studies and because results of other two-year studies find caffeine to be noncarcinogenic in rats. The compound has been withdrawn from consideration of testing by the NTP. (CONTACT PERSON: Dr. W.T. Allaben)

Gentian Violet

90-Day Prechronic Study -- Dose levels in feed for rats and mice were 0, 250, 500, 1000, 1500, and 2000 ppm. There were no deaths. A dose response in reduction of body weight gains was found. Pathological lesions were noted in mice in the lymph nodes, Harderian glands, liver, lung, trachea, and pituitary gland. A final report is on file at NCTR.

Chronic Study - Mice -- Dose levels in feed were: 0, 100, 300, and 600 ppm. Sacrifices were performed at 12, 18, and 24 months (terminal). Mortality was dose-related. Dose-related effects in females were noted for hepatocellular carcinomas, Harderian gland adenomas, erythropoiesis of the spleen, atrophy of the ovaries, and reticulum cell sarcomas (Type A) of the urinary bladder, uterus, ovaries, and vagina. A technical report for this phase of the gentian violet study is on file at NCTR.

Chronic Study - Rats -- Dose levels in feed were: 0, 100, 300, and 600 ppm. Sacrifices were performed at 12, 18, and 24 months (terminal). The data validation, statistical analysis, and data reduction and analysis will be completed in FY 1986 and a final report will be on file the first quarter of FY 1987.

Multigeneration Study - Rats -- Dose levels in feed were: 0, 100, 300, and 600 ppm. The Fla generation only was allocated to the chronic study. Data analysis was completed in FY 1986 and a final report is expected the first quarter of FY 1987. (CONTACT PERSON: Dr. N.A. Littlefield)

Sulfamethazine

90-Day Prechronic Study -- Dose levels in feed for rats and mice were: 0, 300, 600, 1200, 2400, and 3600 ppm. There were no deaths. A dose response was noted with respect to reduction of body weight gain. The mice exhibited no histopathological responses. Examination of the rat data revealed a dose-related response in both males and females for thyroid hyperplasia. A final report is on file at NCTR.

Chronic Study - Mice -- Based on the results from the 90-day study, dose levels in feed were: 0, 300, 600, 1200, 2400, and 4800 ppm. Interval sacrifices were conducted at 12, 18, and 24 months (terminal). Data validation, reduction, and analysis will be completed the first quarter of FY 1987 and a final report will be on file the third quarter of FY 1987.

Chronic Study - Rats -- Based on the 90-day studies, dose levels in feed were: 0, 10, 40, 600, 1200, and 2400 ppm. Interval sacrifices were conducted at 12, 18, and 24 months (terminal). The histopathology examination is scheduled for completion in December 1986. Data validation, reduction, and statistical analysis is expected to be completed the first quarter of FY 1987 and a final report will be on file the fourth quarter of FY 1987.

Multigeneration Study - Rats -- Dose levels in feed were: 0, 10, 40, 600, 1200, and 2400 ppm. Data analysis was completed in FY 1986 and a final report is expected the second quarter of FY 1987. (CONTACT PERSON: Dr. N.A. Littlefield)

1,8-Cineole

Prechronic Study -- Twenty-eight-day repeated dose studies were performed with Fischer 344 male and female rats and B6C3F$_1$ male and female mice. For each species, parallel studies using gavage (rats and mice: 0, 150, 300, 600, and 1200 mg/kg body weight) or microencapsulated compound mixed in the feed (rats and mice: 0, 3750, 7500, 15000, and 30000 ppm) were used to compare possible toxic effects induced via each route of administration. A final report is on file at NCTR.

90-Day Prechronic Study -- Because of budgetary constraints brought on by Gramm-Rudman-Hollings legislation, 90-day prechronic studies will not be performed at the NCTR. (CONTACT PERSON: Dr. George L. Wolff)

Cinnamaldehyde

NTP, in collaboration with Midwest Research Institute, was attempting to obtain encapsulated cinnamaldehyde which was not contaminated with cinnamic acid during the encapsulation process. However, because of Gramm-Rudman-Hollings budgetary constraints, further testing of this compound at NCTR will not be possible. (CONTACT PERSON: Dr. George L. Wolff)

FY 1987 PROGRAM PLANS

The NCTR was faced with budgetary restrictions in FY 1986 which had a significant impact on the level of effort which the Center could give to the National Toxicology Program. No new NTP initiatives are anticipated in FY 1987 given projected FDA/NCTR budgets. The chronic studies with the antihistamines, pyrilamine and triprolidine, will be completed through necropsy and wet tissue storage. Interim reports will be prepared for the antihistamines, doxylamine, pyrilamine, and triprolidine.

NIOSH

TESTING -- LONG-TERM STUDIES WITH EMPHASIS ON OCCUPATIONAL CARCINOGENESIS

NIOSH research emphasizes the identification of occupational environments which may produce cancer and includes: (1) assessment of the carcinogenic potential of complex mixtures encountered by workers; (2) modification of carcinogenesis by known and potential promoters and cocarcinogens that may be part of the work environment such as dusts, irritants, heat and sunlight; and (3) evaluation of factors such as work practices, medications and personal habits which may influence carcinogenicity in the workplace. The intent is to identify needed epidemiology and elucidate the etiology of cancers in the workplace. Identification of carcinogens leads to their control in the workplace.

FY 1986 ACCOMPLISHMENTS

Evaluation of Mesothelioma Production by Asbestos Substitutes -- The project protocol has been successfully peer reviewed. A surgical procedure (modification of the Stanton technique) for placement of an intraplural implant has been developed and tested in a surgical survivability pilot study. The technique will be used to evaluate a respirable size fraction of commercially modified asbestos fibers. (CONTACT PERSON: Mr. F. Platek)

Asphalt Fumes -- Fumes generated at 316^{0}C were separated by high pressure liquid chromatography (HPLC) techniques into five fractions representing 65.5% (aliphatics), 8.1% (thiophenes), 10.6% (phenylethanones and dihydrofuranones), 11.4% (phenols), and 4.4% (aliphatic ketones), respectively, of the 3500 g collected. Skin painting studies were begun to assess the initiating, cocarcinogenic, and promoting potentials of the fumes, the five major fractions, and various combinations of fractions. Preliminary studies were initiated for detailed characterization of the thiophene fraction. (CONTACT PERSON: Dr. T. Lewis)

Dichloroethane: Drug Interactions -- Results from this study completed in FY 1986 indicate that the interaction of 1,2-dichloroethane (EDC) with disulfiram resulted in a high incidence of intrahepatic bile duct cholangiomas in rats of both sexes as well as increased hepatocellular adenomas and testicular tumors in male rats and mammary adenocarcinomas in female rats. The metabolism of EDC was affected by disulfiram treatment resulting in higher blood levels of EDC and increased biological half life. However, DNA binding was not affected by treatment. Separate papers on the chronic toxicity and metabolism were presented at the 1986 Society of Toxicology meeting. (CONTACT PERSON: Mr. K. Cheever)

TEST METHODS DEVELOPMENT AND VALIDATION

Short-Term Carcinogenicity Assays -- The V79 inhibition of metabolic cooperation assay was evaluated by comparing the results from testing 24 tumor promoters and/or cocarcinogens at three contract laboratories. A manuscript has been completed and submitted for publication. Two new contracts were initiated to study the effects of varying culture conditions in the V79 assay system as follows: 1) time of adding 6-thioguanine; 2) calcium chloride concentration; and 3) pH of the medium. Results presented at the Tissue Culture Association meeting in June 1986 indicated that there were no significant differences associated with these variables. The second phase of the two contracts was initiated and an additional thirty promoters and cocarcinogens supplied by NTP will be tested. (CONTACT PERSON: Dr. J. Bohrman)

FY 1987 PROGRAM PLANS

Evaluation of mesothelioma produced by modified asbestos will continue through FY 1987 using a modification of the Stanton intrapleural implantation technique. Skin painting studies assessing the cocarcinogenic and promoting potentials of complete asphalt fumes, the five major fractions, and various combinations of fractions will also continue. Detailed HPLC/GC-MS analysis and characterization of the thiophene fraction will be completed. Approximately 30 additional chemicals will be tested for their effects on metabolic cooperation in the V79 system.

Temporal Factors Influencing Carcinogenicity -- The importance of dose-rate of a suspect carcinogen will be investigated. Ethylene oxide will be used to study the influence of various exposure concentrations (C) and exposure durations (T) (with equal C x T) on carcinogenic potential in rodents. (CONTACT PERSON: Mr. W. Moorman)

TOXICOLOGIC CHARACTERIZATION

Most chemicals selected for NTP toxicology studies are chosen because the potential exists for human exposure and little is known about their toxicologic profile. The toxicologic characterization program attempts to define two principal areas: (1) general toxicology which identifies the toxicity of a chemical by species, sex, dose, and essential organ function; and (2) specific toxicologic effects on the immunological, neurobehavioral, pulmonary, reproductive, and other systems.

The applied activities of the NTP toxicologic characterization program are composed primarily of 14-day, and 90-180 day experiments. These studies are often conducted as part of the prechronic phase of studies described in the Carcinogenesis Research and Applied Studies chapter. Most chemicals selected for chronic (usually two-year) studies are evaluated in a group of genetic toxicity assays to determine potential for inducing gene mutations, chromosome damage, germ cell effects, DNA damage and repair, and cellular transformation, as well as to provide dose-response information. Many are also studied to delineate chemical disposition (absorption, metabolism, distribution, and excretion) patterns in order to improve the scientific knowledge base and the reliability and precision of dose setting for chronic studies. Also, comparative chemical disposition data by multiple routes of exposure may be used to determine appropriate routes of exposure for prechronic and chronic studies. Information is routinely gathered, especially in prechronic studies, related to target organ effects, fertility and reproduction, urinalysis, clinical chemistry and hematology. Morphological assessment -- including tumor pathology, toxicologic pathology, experimental pathology and histology, and electron microscopy -- is an essential component of the toxicologic characterization. Depending on available background information and structure of the chemical, neurobehavioral and immunotoxic potential also may be determined as part of the toxicologic characterization of chemicals.

Research activities in toxicologic characterization are concerned primarily with development and validation of improved assay methods, and with more indepth characterization and understanding of the mechanisms of toxic effects identified in the various study phases (or by others). Specific disciplines and target organ areas include: general and biochemical toxicology, renal toxicology and cardiac toxicology (described in this chapter), chemical disposition, chemical pathology, cutaneous toxicology, immunological toxicology, neurobehavioral toxicology and pulmonary toxicology (described in following chapters). A table of contents of agency activities follows:

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NIEHS

General Toxicology

FY 1986 ACCOMPLISHMENTS

Broadened protocols include measurement of organ weights, more extensive pathology in prechronic experiments, hematology, selected organ function assessment (including liver, kidney, immunologic, reproductive, and neurobehavioral effects), and chemical disposition. The general toxicology screen continues to include efforts to develop and evaluate clinical chemistry procedures for organ function assessment, as well as measures of reproductive function at the end of the 90-day prechronic phase -- testicular morphology, epididymal weights, sperm counts and morphology in male animals, and vaginal cytology in female animals.

The evaluation of the prechronic study results remains a major decision point in the NTP. Results from the 14-day and 90-day studies, along with other information, may indicate that the standard experimental design should be modified, or that detailed special studies (e.g., reproductive toxicology), which would be done separately, are necessary to validate a presumptive toxic effect and to better characterize the toxic potential of the particular chemical. Examples of areas that could be included in special studies are: metabolism, clinical chemistry, hematology, and urinalysis, pharmacokinetics, neurobehavioral toxicology, organ function, immunology, and endocrinology. (These special studies may be integrated into the prechronic or chronic study phases.) The purpose of the special studies varies. They may focus on target organ toxicity, or on problems of comparative toxicology, metabolism, pathology, or physiology which would strengthen the ability to evaluate the animal model selected for the two-year toxicity and carcinogenicity study. In addition, a reanalysis is made at this time of the need for a chronic study. (CONTACT PERSON: Dr. R. Chhabra)

Prechronic Toxicity of Vitamin E Acetate (d-alpha-Tocopheryl Acetate) -- Prechronic (13-week) toxicity studies were conducted by administering d-alpha-tocopheryl (Vitamin E) acetate in corn oil by gavage to two strains of rats (F344 and Sprague-Dawley) maintained on AIN-76 purified diet at daily doses ranging from 125 to 2000 mg/kg body weight. The main compound-related toxic effects noted in these two strains were interstitial inflammation and hyperplasia in the lung and hemorrhagic diathesis. The lung lesions were seen in all dose groups of both strains of rats but the lesion was more severe and more prevalent in the F344 rats. The hemorrhagic syndrome was limited to male and female rats of each strain receiving 2000 mg/kg. To the best of our knowledge, the lung lesions associated with the administration of excess amounts of this vitamin (>125 mg/kg) have not been reported previously. Additional studies are planned to investigate the influence of route of administration (gavage vs. dosed feed) and type of diet (purified vs. natural) on development of Vitamin E induced lung lesions. (CONTACT PERSON: Dr. K. Abdo)

FY 1987 PROGRAM PLANS

Intravenous Toxicity of Vitamin E, Polysorbate 80, and Polysorbate 20 in the Neonatal Rabbit -- The use of Vitamin E in pharmacologic doses has been recommended on a routine basis for the treatment of retrolental fibroplasia and bronchopulmonary dysplasia in premature infants. Recently, an unusual syndrome with fatalities was reported to have occurred in premature infants given intravenous injections of a Vitamin E preparation containing polysorbate 80 and polysorbate 20. Because of this episode the NTP designed a study to investigate the toxic effects of intravenously administered Vitamin E and the polysorbates either individually or in combination in an animal model (neonatal rabbit) which closely mimics the premature infant. Information obtained from this may prove to be essential for the safe use of this type of preparation in the prophylactic treatment of retrolental fibroplasia and respiratory distress syndrome in the human neonate. Results from this study will be reported after completion of histological evaluations of the various tissues. (CONTACT PERSON: Dr. K. Abdo)

Influence of Dietary Restriction on the Prevalance of Neoplastic and Non-Neoplastic Lesions -- One of the criteria used for selecting the highest dose of a chemical to be studied for its carcinogenic potential is a reduction in body weight of no more than 10%. However, it has long been recognized that spontaneous tumor incidence is markedly reduced when body weight is depressed. NTP is currently designing studies to evaluate the influence of 10% reduction in body weight through a moderate (15%) restriction of food intake on spontaneous tumor incidence. The influence of this moderate dietary restriction on the sensitivity of NTP two-year carcinogenicity studies for detecting chemical carcinogens will also be assessed. (CONTACT PERSONS: Dr. K. Abdo and Dr. F. Kari)

Mechanism of Carcinogenicity of HC Blue No. 1 -- In two-year dosed-feed toxicology and carcinogenesis studies conducted by the NTP, there was clear evidence of hepatocarcinogenicity for HC Blue No. 1 in male and female B6C3F1 mice and no evidence of carcinogenicity for HC Blue No. 2 in either sex of B6C3F1 mice. Since these compounds differ only by the presence of a methylamino group (HC Blue No. 1) compared to a hydroxyethylamino group (HC Blue No. 2), new studies have been initiated in the Experimental Toxicology Unit, Carcinogenesis and Toxicology Evaluation Branch (CTEB), to determine whether absorption, metabolism, and/or excretion might differently influence the carcinogenic potential of these compounds. (CONTACT PERSON: Dr. F. Kari)

Biochemical Toxicology of Methylphenidate -- Methylphenidate, a central nervous system stimulant, has been shown to be hepatotoxic in prechronic toxicity studies. The structure of methylphenidate does not suggest that it would be a hepatotoxicant; thus, studies have been designed for the Experimental Toxicology Unit, CTEB, to a) determine if methylphenidate toxicity is a result of bioactivation and, if so, to determine which enzyme systems are involved, b) determine the nature of the putative activated toxic metabolite of methylphenidate, and c) determine the effect of methylphenidate on xenobiotic metabolizing and protective systems of the liver. (CONTACT PERSON: Dr. E. Rauckman)

FY 1986 ACCOMPLISHMENTS

Toxicity Studies of NPPD -- In response to concerns that American diplomatic staff and their families in the USSR might have been exposed to "spy dust" (NPPD)(5-(4-nitrophenyl)-2,4-pentadien-1-al), skin-paint and oral toxicity studies were designed to determine possible target organs, no observable effect levels, and effects of route of administration. The skin-paint study has been completed.

FY 1987 PROGRAM PLANS

An oral toxicology study of NPPD is scheduled for FY 1987. (CONTACT PERSON: Dr. E. Rauckman)

FY 1987 PROGRAM PLANS

Dermal Absorption of Diethanolamine and Triethanolamine -- Diethanolamine and triethanolamine are widely used in cosmetic products such as creams, lotions, skin cleaners, and shampoos. The NTP is presently conducting prechronic dermal toxicity studies of these compounds in F344 rats and B6C3F1 mice. Dermal absorption studies in rats and mice are also being performed in the Experimental Toxicology Unit, CTEB, to help interpret results of the prechronic toxicity studies and to aid in the selection of dose levels for possible chronic dermal studies of these chemicals. (CONTACT PERSON: Dr. R. Melnick)

FY 1986 ACCOMPLISHMENTS

Mechanism of 1,2-Dibromo-3-chloropropane (DBCP)-induced Male Infertility -- The nematocide, DBCP, has been causally associated with lowered sperm counts and infertility in male pesticide workers. Recent studies indicated that a nearly immediate infertility may result from a direct effect of DBCP on post-testicular sperm. A specific site of inhibition of carbohydrate metabolism by DBCP on post-testicular sperm has been identified in in vitro studies as the NADH dehydrogenase step of the mitochondrial electron transport chain.

FY 1987 PROGRAM PLANS

Further studies on DBCP in the Experimental Toxicology Unit, CTEB, are planned to correlate in vitro and in vivo findings and to evaluate whether a similar mechanism of action occurs at other target organs. (CONTACT PERSONS: Dr. R. Melnick and Mr. A. Greenwell)

Application of Microencapsulation for Toxicology Studies

The use of microencapsulation as an alternative means of incorporating volatile, reactive and/or unpalatable chemicals into rodent feed for toxicologic studies has been evaluated by the NTP. Encapsulation of trichloroethylene in gelatin-sorbitol microcapsules provided a high level of stability to this volatile chemical and did not alter its bioavailability in rats. 2-Ethyl-1-hexanol has recently been stabilized in food grade corn starch microcapsules.

FY 1987 PROGRAM PLANS

Bioavailability and toxicology studies of microencapsulated 2-ethyl-1-hexanol will be conducted. (CONTACT PERSONS: Dr. R. Melnick, Dr. T. Goehl, and Dr. C.W. Jameson)

Renal Toxicology

FY 1986 ACCOMPLISHMENTS

In Vitro Assays for Nephrotoxicity -- Studies have begun to develop and refine techniques for culturing various sections of kidney tubules which will be used in *in vitro* testing of chemicals for kidney cell toxicity. Culture techniques are being developed and determinations are being made of endpoints which will be used as indicators of renal toxicity.

FY 1987 PROGRAM PLANS

The development of culture techniques will continue in FY 1987, and mechanistic studies using isolated kidney cell fractions will be performed after these techniques have been perfected. (CONTACT PERSON: Dr. E. J. Rauckman)

Fischer 344 Rat Leukemia Model

Use of the Fischer 344 rat leukemia model in a short-term test system may provide another sensitive measure of determining potential chemical hazards to man. In addition, this animal model may provide information regarding the cellular toxicity of chemicals used to treat leukemia that may be useful in therapeutic interventions. Having the capability to discriminate between age-induced leukemia (spontaneous tumor or normal background incidence) and chemically-enhanced or induced leukemia will increase the sensitivity and accuracy of tests for chemical carcinogens in the F344 rat.

FY 1986 ACCOMPLISHMENTS

Fischer rat leukemia is being maintained *in vivo* by serial transplantation into 6-8 week old male F344 rats (syngeneic recipients) every 60-90 days. At each successive transplant series spleen cells from several leukemic rats are collected, separated and enriched on density gradients. The leukemic mononuclear cell fractions are counted and an aliquot is frozen for later evaluation of transplant efficacy and degree of potency. Potency of the leukemic mononuclear spleen cells from the serial transplants were compared simultaneously in syngeneic recipients; time to mortality decreased with the number of passages from 100+ days in transplant series 1 down to 80+ days by series 4.

The efficacy of the Fischer rat leukemia transplant model for detecting chemical leukemogenesis is being evaluated with chemicals that have been previously tested in NTP chronic toxicology and carcinogenesis studies. Pyridine was shown to cause an increased incidence of leukemia over control levels in two-year studies while treatment with 2-ethoxyethanol resulted in complete elimination of the 20-40% background incidence of leukemia seen in untreated controls. These first two chemicals are being studied to compare their toxic effects and their effects on the expression of transplanted leukemia. At 60 and 90 days post-transplantation blood and spleen samples will be taken to verify the course of the leukemia, to evaluate the efficacy of the leukemia transplant model, to discriminate between chemical effects and to determine the utility of selected biochemical tumor markers as early detectors of leukemia.

FY 1987 PROGRAM PLANS

The leukemia research project in F344 rats will include an investigation of the isozymes of acetylcholinesterase and malate dehydrogenase that are markers for leukemia in the F344 rat. Additional chemicals that are known to have caused an increased incidence of leukemia in chronic tests, including 2,4,6-trichlorophenol and dimethylmorpholinophosphoramidate, will be used in the rat leukemia model to determine the efficacy of this system for detecting chemical effects on leukemogenesis in a 60-90 day period. The relationship between hepatocellular tumor increase and concommitant leukemia decrease in the F344 rat in certain NTP studies will be investigated by *in vitro* and *in vivo* methods to determine whether there may be release of inhibitory factors from the hepatocellular tumor. The nature of the splenic involvement in the etiology of Fischer rat leukemia will also be investigated in splenectomized and chemically-treated rats. (CONTACT PERSONS: Dr. M.P. Dieter and Dr. J.E. French)

Metal Toxicology

The effects of inorganic or organic metals and metal complexes are of particular interest to the NTP because of their prevalence in drinking water and industrial processes, use as constituents in anticancer drugs, and their diverse target organ toxicities.

FY 1986 ACCOMPLISHMENTS

Nickel Sulfate -- This metal salt was not immunotoxic to female B6C3F1 mice exposed through the drinking water but exerted a major effect on myelopoiesis, causing a reduction in bone marrow cellularity and a decrease in stem cell proliferation capability. There were biochemical effects correlated with the myelotoxicity that indicated the hexose monophosphate shunt enzymes in the bone marrow cells were inhibited by nickel sulfate and that, as in previous studies of myelotoxic chemicals, the colony forming units of granulocytes and macrophages were the major cell fractions affected, since enzymatic inhibition was confined to this cell population in the bone marrow. (CONTACT PERSON: Dr. M.P. Dieter)

Nickel Compounds -- The NTP has initiated studies to help understand the mechanisms of metal carcinogenicity and the relative carcinogenicity of water soluble and insoluble metals. In progress are toxicology studies in which nickel oxide (NiO) (insoluble), nickel sulfate ($NiSO_4$)(soluble), and nickel subsulfide (Ni_3S_2) (insoluble) are administered by the inhalation route to rats and mice. Results from two-week studies show the toxicity ranking of the nickel compounds are $NiSO_4 > Ni_3S_2 >> NiO$. Endpoints that are being analyzed include effects on the immune system, enzyme alterations, hematology and urinalysis, and pathologic effects. The effects seen will be correlated with the relative tissue distribution of the metals. (CONTACT PERSON: Dr. J. Dunnick)

FY 1987 PROGRAM PLANS

Mercuric Chloride -- Urinary enzyme responses were measured in rats and mice after exposure by gavage to mercuric chloride for two years and the extent of the correlation between renal pathology and the biochemical responses will be evaluated at the end of this chronic study. (CONTACT PERSON: Dr. M.P. Dieter)

Titanocene Dichloride -- Titanocene accumulation in tissues evaluated at different intervals in two-year toxicology and carcinogenesis studies will be compared with lesions in these tissues at study termination. Spleen samples were collected from contract laboratory animals and mononuclear cell samples separated and frozen for later enzyme analyses. Blood samples were evaluated for evidence of leukemia. Glucose metabolizing enyzymes and acetylcholinesterase will be evaluated in the spleen mononuclear cells to correlate with histopathological evidence and to evaluate their utility as marker enzymes for leukemia. (CONTACT PERSON: Dr. M.P. Dieter)

Antimony Potassium Tartrate(APT) -- Toxic responses to APT will be compared in rats and mice dosed for 14 days by either intraperitoneal (i.p.) injection or in the drinking water, and the degree of accumulation of antimony in blood, liver, kidney, heart, and spleen will be correlated with target organ toxicity. These data will be used to select a route of administration and doses for 13-week studies and to guide expanded studies on appropriate target organs. (CONTACT PERSON: Dr. M.P. Dieter)

Chromates (Sodium Chromate, Zinc Potassium Chromate, and Chromium Carbonyl) -- A collaborative research project will determine prechronic toxicity, help set chronic dose levels, and perhaps aid in deciding whether only one of the three chromate salts needs to be evaluated in two-year studies. After repeated i.p. injections of $B6C3F_1$ mice with the three salts, blood will be collected at intervals to perform micronuclei analyses, and bone marrow samples will be taken to compare the toxic effects of the three chromates on cellularity and stem cell proliferation rates and cellular biochemical responses, and for analysis of chromium residues. Bone marrow will also be used to analyze for the incidence of sister chromatid exchanges and chromosomal aberrations in mice after single treatment with the three salts. (CONTACT PERSON: Dr. M.P. Dieter)

Ferric ammonium ferrocyanide (FAF) -- The acute toxicity and/or absorption of FAF will be evaluated in rats and mice and the data obtained will help determine the appropriateness of subsequent pharmacokinetic or metabolism studies, and the necessity for any prechronic testing. (CONTACT PERSON: Dr. M.P. Dieter)

Methods Development -- Studies will be aimed at enhancing the stability, sensitivity, and efficiency of the assay for 7-ethoxycoumarin-ortho-demethylase enzyme activity. The assay will be used to evaluate activation by chemicals of mixed function oxidases (MFOs) in minute amounts of rodent tissue. The method will be applied in liver, spleen, and bone marrow of mice and rats to measure comparative enzymatic rates in these tissues and to evaluate the sensitivity necessary for optimal measurement of enzyme activities. (CONTACT PERSON: Dr. M.P. Dieter)

Nickel Compounds -- During FY 1987, chronic studies to compare the carcinogenicity of NiO, $NiSO_4$, and Ni_3S_2 in F344/N rats and B6C3F1 mice will be initiated. (CONTACT PERSON: Dr. J. Dunnick)

Cobalt Sulfate -- Cobalt sulfate is a water soluble salt currently under prechronic testing by inhalation. Special studies include assessments of potential neurobehavioral, hematologic and nephrotoxic effects. (CONTACT PERSON: Dr. J. Bucher)

Neurotoxicity

FY 1987 PROGRAM PLANS

The NTP conducts most of its toxicology and carcinogenicity studies in rats and mice, and analysis of studies in rodents often indicates the potential for neurotoxicity. Studies of certain chemicals (e.g., dimethyl methyl phosphonate) have shown evidence of neurotoxicity and investigations are in progress to evaluate the neurotoxic potential of this chemical in hens, a species that is particularly sensitive for this endpoint. (CONTACT PERSON: Dr. J. Dunnick)

Butadiene Initiative

FY 1986 ACCOMPLISHMENTS

1,3-Butadiene is a high production chemical which is used largely as an intermediate in the production of synthetic rubber. In a recent NTP chronic inhalation study, butadiene was found to induce neoplastic lesions at multiple target sites in male and female B6C3F1 mice at exposure levels below the threshold limit value (1000 ppm) for this chemical. Additional inhalation toxicology studies have begun to characterize dose-response relationships for butadiene-induced neoplastic and nonneoplastic lesions in mice (exposure concentrations range from 6.25 to 625 ppm), to assess the relationship between exposure level and duration of exposure on the outcome of butadiene induced carcinogenicity, and to characterize the toxicity of butadiene in rats.

FY 1987 PROGRAM PLANS

Prechronic inhalation toxicity studies of two structural analogs of butadiene, chloroprene (2-chloro-1,3-butadiene) and isoprene (2-methyl-1,3-butadiene), will be started in FY 1987. An update on chemical disposition studies of isoprene and 1,3-butadiene may be found in the Chemical Disposition chapter. (CONTACT PERSON: Dr. R. Melnick)

Phthalate Studies

FY 1986 ACCOMPLISHMENTS

Mechanism of Di(2-ethylhexyl)phthalate-induced Hepatotoxicity -- In two-year toxicology and carcinogenesis studies conducted by NTP, di(2-ethylhexyl)-phthalate (DEHP) was found to be hepatocarcinogenic in F344 rats and B6C3F1 mice. It has been suggested that the hepatocarcinogenicity of DEHP and other peroxisome proliferators may be due to an excessive production of hydrogen peroxide (H_2O_2) during enhanced peroxisomal b-oxidation. Last year, increases in peroxisomal steady-state levels of H_2O_2 were demonstrated in liver homogenates prepared from rats or mice treated with DEHP or nafenopin, a hypolipidemic drug. Further studies indicated that acyl CoA oxidase was the most suitable marker for early peroxisomal changes induced by DEHP and that the apparent no-observable effect level for this change in rats is 60 mg/kg/day.

FY 1987 PROGRAM PLANS

Studies are in progress in the Experimental Toxicology Unit, CTEB, to characterize lipid peroxidation in isolated hepatocytes treated with DEHP and nafenopin and to determine structural requirements for chemical induction of peroxisome proliferation. (CONTACT PERSONS: Dr. R. Melnick and Dr. K. Tomaszewski)

Superfund Project

(Interagency Agreement Between the Agency for Toxic Substances and Disease Registry and the National Toxicology Program)

Under an interagency agreement between the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Toxicology Program (NTP), the NTP participates in the Public Health Service activity related to the Comprehensive Environmental Responses, Compensation and Liability Act (Superfund Act) by conducting toxicology testing on chemicals that were identified in priority hazardous waste sites or otherwise released into the environment for which adequate toxicology data may not be available.

The chemicals that NTP agrees to test are selected from among those that EPA identified as being present in priority hazardous waste sites. These chemicals were nominated for NTP testing by EPA, the Hazardous Waste Information Evaluation Subcommittee (HWIES) of the DHHS Committee to Coordinate Environmental and Health Related Programs and/or the NTP Chemical Evaluation Committee. The necessity, nature, and scope of testing is determined by NTP in accordance with the Program's established procedures.

FY 1986 ACCOMPLISHMENTS

Part I. Individual Chemical Evaluation and Studies -- At the end of FY 1986, NTP Superfund activities with regard to the individual chemical literature evaluation and data-gap filling are shown as follows:

Status	Number of Chemicals*
A. Reviewed by the Toxicology Design Committee	14
B. Reviewed, deferred	2
C. Contract negotiation/award	30
D. Studies in progress	33
E. Chemicals with one or more studies completed	22

*Includes isomers and selected chemicals under a general group such as the phthalates.

(CONTACT PERSONS: Dr. E. J. Rauckman and Dr. R. S. H. Yang)

Part II. Toxicity Studies on Chemical Mixtures of Environmental Concern --

1. Chemical Mixtures of Environmental Concern

A research proposal has been approved by the TRTP Management Committee, and has been peer-reviewed internally and externally. This proposal is aimed at the investigation of the combined toxic effects in laboratory animals following repeated and pre-chronic ingestion in drinking water, of some of the more frequently occurring drinking water contaminants (28 organic and inorganic chemicals). This proposal is at the stages of chemistry developmental work and Request for Proposal (RFP) preparation. (CONTACT PERSON: Dr. R.S.H. Yang)

2. *In Vitro* Toxicity Testing of Chemical Mixtures

The objective of this project is to screen possible joint toxic actions of chemical mixtures using primary hepatocyte cultures and to investigate mechanistic aspects of cellular joint action. In-house development of techniques for the primary cell culture is in progress. (CONTACT PERSON: Dr. E.J. Rauckman)

3. Toxicological Interactions of Binary Mixtures

An in-house effort has been initiated to conduct pilot studies to explore the joint toxicity of binary mixtures *in vivo* based on known toxic mechanisms using target organs such as liver, kidney, the nervous system and the reproductive organs. The first project, which began in the second quarter of FY 1986 in the Experimental Toxicology Unit, CTEB, involves the study of the potential toxicological interactions of hexachloro-1,3-butadiene and chloroform. The selection of these two chemicals was based on their known renal and hepatic toxicities and the biochemical mechanisms involved. (CONTACT PERSON: Dr. R.S.H. Yang)

FY 1987 PROGRAM PLANS

Part I. Individual Chemical Evaluation and Studies -- Work will continue on the individual chemical literature evaluation, the identification of data-gaps, and conducting experimental work on contract to fill the data-gaps on the chemicals listed in Table 16. Additional chemicals with specific needs for study are anticipated. The progress of each chemical is updated quarterly and a status report is submitted to ATSDR. For detailed information on the status of any given chemical in Table 16 contact the NTP. (CONTACT PERSONS: Dr. E.J. Rauckman, Dr. R.S.H. Yang and Ms. J. Guthrie)

Part II. Toxicity Studies on Chemical Mixtures of Environmental Concern -- Studies on the toxicity of chemical mixtures as reported for FY 1986 will continue at a higher level of activity in FY 1987.

1. Chemical Mixtures of Environmental Concern

   The RFP for the repeated-dose and prechronic studies of a mixture of 28 chemicals in drinking water will be issued and a contract award is expected to be made during FY 1987. Additional protocols for investigation of the frequency of toxicological interaction among selected chemicals will be developed. (CONTACT PERSON: Dr. R.S.H. Yang)

2. *In Vitro* Toxicity Testing of Chemical Mixtures

   In-house development of techniques for the primary cell culture will continue in FY 1987. (CONTACT PERSON: Dr. E.J. Rauckman)

3. Toxicological Interactions of Binary Mixtures

   In-house effort will continue on the studies to explore the joint toxicity of binary mixtures *in vivo* based on known toxic mechanisms using target organs such as liver, kidney, the nervous system and the reproductive organs. The first project examining joint renal and hepatic toxicities of hexachloro-1,3-butadiene and chloroform will continue. Additional binary mixtures will be selected for investigation in the Experimental Toxicology Unit, CTEB. (CONTACT PERSON: Dr. R.S.H. Yang)

4. Physiologically Based Pharmacokinetics/Computer Modeling "Skill Center"

   Considering the infinite number of probable combinations for the chemicals in the hazardous waste sites, the need to utilize computer based models of physico-chemical and biological processes (e.g., physiologically based pharmacokinetic models) to aid in the elucidation of the toxicology of chemical mixtures is obvious. An effort has been initiated to develop a "skill center" in this very important area for the Superfund effort. (CONTACT PERSON: Dr. R.S.H. Yang)

The Benzidine-Dye Initiative

The benzidine-dye initiative was designed to study the toxicology and carcinogenicity of a class of dyes derived from either benzidine, 3,3'-dimethylbenzidine, or 3,3'-dimethoxybenzidine. This group of dyes includes some 82 discrete chemicals which are available in the United States. Because of the high cost and time requirements for long-term studies in rats and mice, no attempt was made to routinely evaluate all benzidine and benzidine congener dyes in the NTP program. Instead, an interdisciplinary chemical class toxicology program was designed and studies began in FY 1981, and continue. Table 17 summarizes the types of studies and status of the studies for those benzidine congeners selected.

The program was developed in response to the needs of EPA, CPSC, and OSHA. The scientific objectives and approaches were formulated by scientists from the EPA, CPSC, OSHA, NCI, NIEHS, NCTR, and NIOSH. As designed, the program has provided scientific information required for making regulatory decisions about benzidine and benzidine congener-based dyes and served as a model for other chemical class studies. One such initiative (aminobenzothiazoles) is described below. (CONTACT PERSON: Dr. J.H. Mennear)

NIEHS

FY 1986 ACCOMPLISHMENTS

CI Direct Blue 218 -- The two-year toxicology and carcinogenesis studies started in FY 1985 continue.

CI Direct Blue 15 -- Initial histopathological evaluation has been completed and a preliminary draft technical report has been received.

CI Acid Red 114 -- The two-year toxicology and carcinogenesis studies were completed, initial histopathology was finished, and a preliminary draft technical report has been received.

Dimethyl- and Dimethoxybenzidine -- Initial histopathology was completed and preliminary draft technical reports were received.

Tumor Transplant Study -- An evaluation of the transplantability of tumors produced by dimethylbenzidine and C.I. Direct Blue 15 was initiated in FY 1984. The tumors have been through four passes and the final group of animals is being observed.

Aminobenzothiazole Toxicity Initiative -- Aminobenzothiazoles are a class of chemicals which are used as chemical intermediates. In particular, they find use in the production of monoazo dyes. Three of these compounds were selected as NTP priority chemicals in FY 1984. Two other members of this class were subsequently selected for toxicity studies in rats and mice in order to better define the structure-toxicity relationship for this class of chemicals. Sixteen compounds were selected for study in Salmonella to determine the mutagenic activity and aid in defining the structural features of these compounds which influence this activity.

Repeated dose studies (14-day) on rats and mice were completed for four of the five compounds selected for prechronic studies. Results were reviewed and dose levels for the 13-week studies were established. *Salmonella* mutation studies were completed for most of the 16 chemicals selected. However, results will not be reviewed until all compounds have been completed. (CONTACT PERSON: Dr. E.J. Rauckman)

FY 1987 PROGRAM PLANS

In Vivo Toxicology and Carcinogenicity Studies -- Final draft Technical Reports are planned in FY 1987 for dimethylbenzidine, dimethoxybenzidine, C.I. Direct Blue 15 and C.I. Acid Red 114. These reports were delayed because of an unexpectedly large number of tissues requiring extensive histopathological evaluation.

Tumor Transplant Study -- Final reports from the contract laboratory will be received during FY 1987. The results of these studies will be published in the scientific literature and will be incorporated into the technical reports mentioned above.

Aminobenzothiazole Toxicity Initiative -- Thirteen-week studies in rats and mice will be completed for all five of the selected aminobenzothiazoles in FY 1987. Determination of the necessity to conduct further studies will be made on the basis of these results. Testing on all of the 16 chemicals selected for mutagenesis studies will be completed in FY 1987 and the results reviewed. These results will be used to plan possible subsequent studies to better determine the structure-activity relationship of this class of chemicals. (CONTACT PERSON: Dr. E.J. Rauckman)

TABLE 16

SUPERFUND CHEMICALS REVIEWED IN FY 1986

I.	First Group:	CAS No.
1.	Aniline	62-52-3
2.	Benzene	71-43-2
3.	Bromoform	75-25-2
4.	Carbon Tetrachloride	56-23-5
5.	Chlorobenzenes (mono-,di)	-
6.	1,2-Dichloroethane	107-06-2
7.	Dichloroethylenes	-
8.	Dichloromethane	75-09-2
9.	1,2-Dichloropropane	78-87-5
10.	Ethyl Benzene	100-41-4
11.	Ethylene glycol	107-21-1
12.	Hexachlorobenzene	118-74-1
13.	Hexachloro-1,3-butadiene	87-68-3
14.	n-Hexane	110-54-3
15.	Methyl ethyl ketone	78-93-3
16.	Pentachlorobenzene	608-93-5
17.	Phthalates	-
18.	1,1,2,2-Tetrachloroethane	79-34-5
19.	Tetrachloroethylene	127-18-4
20.	Tetrahydrofuran	109-99-9
21.	Toluene	108-88-3
22.	1,1,1-Trichloroethane	71-55-6
23.	Trichloroethylene	79-01-6
24.	Xylenes	1330-20-7

II.	Second Group:	CAS No.
1.	Acetone	67-64-1
2.	Cresols	1319-77-3
3.	Cupric sulfate	7758-99-8
4.	Sodium cyanide	143-33-9
5.	Sodium selenate	13410-01-0
6.	Sodium selenite	10102-18-8
7.	1,2,4,5-Tetrachlorobenzene	95-94-3

TABLE 17

SUMMARY OF THE NTP BENZIDINE CONGENER INITIATIVE

Chemical	CAS No.	Studies[1]
Benzidine derived		
Benzidine	92-87-5	G,P,T[2]
C.I. Direct Blue 6	2602-46-2	G,P,T[2]
o-Dianisidine derived (3,3'-dimethoxybenzidine)		
o-dianisidine	119-90-4	G,P,T[3]
C.I. Direct Black 114	61703-05-7	G,M
C.I. Direct Blue 8	2429-71-2	G,M
C.I. Direct Blue 10	4198-19-0	G,M
C.I. Direct Blue 15	2429-74-5	G,P,T[3],M
C.I. Direct Blue 218	28407-37-6	G,P,T[4]
C.I. Direct Violet 32	6428-94-0	G,M
o-Tolidine derived (3,3'-dimethylbenzidine)		
o-tolidine	119-93-7	G,P,T[3]
C.I. Acid Red 114	6459-94-5	G,P,T[3]
C.I. Direct Blue 14	72-52-1	M
C.I. Direct Blue 25	2150-54-1	G
C.I. Direct Blue 53	314-13-6	G,M
C.I. Direct Orange 6	6637-88-3	G,M
C.I. Direct Red 2	992-59-6	G,M
C.I. Direct Red 39	6358-29-8	G,M

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[1] Key:
G = Genetic toxicology assays - all planned studies completed
P = Pharmacokinetic studies - all planned studies completed
M = Metabolism studies for detection of carcinogens in urine - completed
T = toxicologic and carcinogenesis studies

[2] Benzidine and Direct Blue 6 were comparatively studied in a 13-week feeding study in rats only.

[3] o-Tolidine, Acid Red 114, o-Dianisidine and Direct Blue 15 are being comparatively evaluated in two-year toxicology and carcinogenesis studies in rats only. In-life studies were completed in FY 1985 and initial histopathology was completed during FY 1986.

[4] Direct Blue 218 was tested in rats and mice in a 13-week study. Data from this study and genetic toxicology studies were used to determine that two-year toxicology and carcinogenesis studies were indicated. In-life studies were started in FY 1985.

NIOSH

FY 1986 ACCOMPLISHMENTS

Cardiac Toxicology -- Six-month inhalation exposures of rats to carbon disulfide (CS_2) were completed. It was originally hypothesized that CS_2 induced coronary heart disease by affecting thyroid function, which would lead to elevated serum lipids causing atherosclerosis. Serum lipids, however, were not elevated in rats exposed to CS_2 for up to six months. (CONTACT PERSON: Mr. D. Lynch)

Cellular and Molecular Cardiac Toxicology -- A program was initiated for the study of cardiac toxicity *in vitro* using cultured heart cells. Methods were developed for harvest and plating of isolated cells from neonatal rats. Primary cultures of cardiac myocytes form a confluent monolayer that beats rapidly and rhythmically as a syncytium. Cultured cells will be used to evaluate cardiac toxicity at the cellular level. A protocol was also developed for using isolated mitochondria to screen for cardiotoxins. (CONTACT PERSON: Dr. M. Toraason)

FY 1987 PROGRAM PLANS

Cardiac Toxicology -- The role of cardiac glutathione depletion on the pathogenesis of allylamine-induced cardiac fibrosis and necrosis will be evaluated in F-344 rats. Cardiac toxicity will be assessed using morphological (gross and histopathology), biochemical (serum enzymes), and functional indices (electrocardiography), and the incidence and severity of toxicity will be correlated with cardiac glutathione concentrations. (CONTACT PERSON: Mr. D. Lynch)

Cellular and Molecular Cardiac Toxicology -- Isolated heart cells will be evaluated for their ability to replicate cardiac responses occurring in the intact animal. Contractile responses will be measured following treatment with drugs, hormones and various agonists and antagonists. Cardiac mitochondria will also be evaluated as a potential screen for cardiotoxins. The screen will be based on the ability of xenobiotics to inhibit electron transport and oxidative phosphorylation. (CONTACT PERSON: Dr. M. Toraason)

CHEMICAL DISPOSITION

The immediate objective of chemical disposition studies is to provide information on the absorption, distribution, metabolism and excretion of chemicals or chemical classes chosen for evaluation by the NTP. This information is intended for use in the design, choice of dose and interpretation of results from studies of the toxicity and carcinogenicity of these chemicals. Long-range, but equally important, objectives of chemical disposition studies are to develop and publish data that will permit a better assessment of structure-activity relationships which influence chemical disposition or mechanisms of toxicity and provide basic information for facilitating the extrapolation of laboratory data to man. Another objective is development of analytical methodology and data on metabolism and use of this information in evaluating disposition in workers exposed to chemicals. A table of contents of agency activities follows:

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NIEHS

Studies of chemical metabolism and disposition conducted during FY 1986 have addressed or are currently addressing the fate of a number of different chemicals in one or more species. The list of compounds studied includes both organic and inorganic chemicals and study design for these chemicals has varied according to 1) the need for data regarding chemical structure, properties or dose; 2) tests for acute or chronic toxicity. These types of studies established that exposure to some highly halogenated compounds is limited by the fact that these compounds are very sparingly absorbed from the gastrointestinal tract. Other compounds were determined to be readily absorbed from the gastrointestinal tract but poorly absorbed from the skin and still others were shown to be very readily absorbed from both sites. Four volatile compounds were shown to be absorbed from the lung following inhalation. Studies of one of these compounds, 1,3-butadiene, are providing data which will prove useful in assessment of human risk in industrial exposure. An indepth multiyear study of benzene is providing data on the fate of this compound administered at a wide range of doses and should prove useful for risk assessment of health effects for a large segment of the general public.

In addition to general studies of chemical disposition, this group is conducting several projects to address special problems. Among these special studies is a study of the teratogenicity of halogenated dioxins and furans. These studies indicate that the teratogenicity of these compounds may be potentiated when they are administered in combination with certain other chemicals such as polychlorinated biphenyls. Other special studies are addressing the toxicity of a series of chemicals which when administered alone or in combination with other chemicals may antagonize or potentiate their toxic effects. Of particular relevance to the NTP studies of chronic toxicity are studies which demonstrate senescent changes in xenobiotic metabolism and disposition by rats. Of particular relevance to human risk assessment are the efforts to develop methods to assess chemical metabolism in human tissues. The following is a list of accomplishments in these areas.

FY 1986 ACCOMPLISHMENTS

1. The fate of citral (oil of lemon) has been studied in male F344 rats. This chemical, a mixture of two isomers, geraniol and nerol, occurs in detergents, cosmetics, and foods. Citral is highly unstable and undergoes spontaneous oxidation on storage. Therefore, it requires repurification, immediately before use. We are studying the effects of dose on oral absorption and excretion in male F344 rats. Urine appears to be the major route of excretion with substantial amounts of $^{14}CO_2$ also being excreted. With little unmetabolized citral being exhaled unchanged, feces is a minor route of excretion. The effect of dose on dermal absorption will also be investigated. Distribution and metabolism will be studied after i.v. exposure. Differential absorption and metabolism of the two isomers will be looked for as will the effect of repeated exposure to citral on its disposition.

2. Dermal absorption of the rubber antioxidant, 4,4'-thiobis-(6-t-butyl-m-cresol) was investigated in comparative studies in male Fischer 344 rats and in Sencar mice. Absorption is very limited with only 6% of the dose (5 mg/kg by corn oil gavage) being absorbed by rats and 20% by mice. Once absorbed, excretion routes were similar to that previously observed after i.v. exposure. Increasing the dose resulted in decreased absorption as the chemical crystallized out at the site of application.

3. Studies of the comparative metabolism and disposition of ethyl carbamate have been completed in rats and mice. Results of these studies indicate that whereas the mouse has the greater capacity to metabolize this compound to CO_2, metabolism follows similar pathways in both species. Metabolism appears to be the limiting factor for clearance by both species and very little parent compound is excreted. It appears that much of the previously available literature on this chemical has been obtained at doses which saturate the metabolic capacities of both species. Metabolism studies of this chemical indicate that

the carboxyesterase enzymes thought to metabolize this compound may not be involved in its metabolism; rather metabolism may result from a nonspecific interaction of chemical and protein. The net result of this interaction is a complex set of kinetics which describes the clearance of ethyl carbamate. The nature of the species dependent variation in metabolism of ethyl carbamate has been clearly identified and quantitated, but the mechanisms involved have not yet been elucidated. Work to this end is continuing.

4. Studies of the pharmacokinetics of 2-butoxyethanol (2BE) indicate that it is readily absorbed from all routes, including the skin. On absorption, 2BE has an unusual toxicity to red blood cells causing massive hemolysis at moderate doses. Investigation of the hemolytic effects of 2BE has determined that they are not only dose dependent, but the effect becomes more pronounced as the age of the exposed animal increases. Further, these hemolytic effects and the associated kidney and liver damage are inhibited by pretreatment with inhibitors of 2BE metabolism. Metabolism of 2BE results in excretion in urine and in exhaled air as CO_2. Only a trace of the dose was excreted in feces. Metabolism in young adult rats is saturated at doses above 200 mg/kg resulting in altered metabolism and excretion. Ongoing investigations are designed to determine the metabolites and mechanisms of toxicity.

5. 2-Butoxyethanol (BE) hematotoxicity and the effects of age and metabolism are being investigated in F344 rats. Gavage administration of a single dose of BE caused a dose-dependent decline in the number of circulating red blood cells, hemoglobin concentration and hematocrit. This hemolytic effect of BE was accompanied by an increase in spleen weight/body weight ratio, free plasma hemoglobin levels and the development of hemoglobinuria. Furthermore, at the high dose (500 mg/kg) BE caused secondary liver necrosis and kidney changes. All these effects of BE were age-dependent with the young rats being less sensitive than older rats. Doses of 125 mg/kg of BE by gavage for eight consecutive days revealed a gradual decrease in the hemolytic effects of BE. In addition, hemoglobinuria was seen after the first dose only, but not after following doses. This is indicative of development of tolerance. Tolerance to BE toxicity was attributed to a decline in the hemolytic effects of BE with multiple dosing.

6. Comparative studies of resorcinol disposition in male and female rats following doses of 112 mg/kg resulted in 84% of the dose being excreted in urine, 8% in feces and very little retention in tissues. Little sex-related difference was observed in disposition or clearance. Chromatographic resolution of the metabolites excreted in urine indicates that each sex forms the same four polar metabolites and excretes only a trace of parent compound. There is some sex-related variation in the relative amounts of the minor metabolites formed, but the major metabolites are formed in similar amounts. The metabolites have been tentatively identified as sulfate and glucuronide conjugates of resorcinol. Ongoing work is designed to determine the effect of increased doses in saturating or inhibiting conjugating enzymes.

7. Studies of the effects of repeat dosing with ethyl acrylate (EtAC) on the rat forestomach indicate that daily gavage administration of EtAC to male

F344 rats for two weeks resulted in papillomatous thickening of the forestomach. Microscopic examination revealed several forestomach lesions which included mucosal hyperplasia and hyperkeratosis. Investigation of the recovery of these and other lesions revealed that all forestomach lesions caused by 100 mg/kg EtAC disappeared within 14 days after the last dose. However, forestomach lesions caused by 200 mg/kg EtAC only regressed in the same time period. By four weeks after the last dose, all lesions had disappeared except EtAC-induced forestomach hyperplasia. Further, at the end of the four-week recovery period, two additional histopathologic lesions, namely, fibrosis and foreign body reactions, were seen in rats treated with the high dose of EtAC.

8. The teratogenicity of 2,3,4,7,8-pentachlorodibenzofuran (4-PeCDF), 1,2,3,7,8-pentachlorodibenzofuran (1-PeCDF), and 1,2,3,4,7,8-hexachlorodibenzofuran (HCDF) has been investigated in C57BL/6N mice. The dose response curves for teratogenic effects were very steep and parallel to that previously observed for TCDD. The ED_{50} for cleft palate was approximately 40 µg/kg for 4-PeCDF, 100 µg/kg for 1-PeCDF, and 400 µg/kg for HCDF. The no effect level (NOEL) for hydronephrosis, which occurred at doses below that causing cleft palate, was 1 µg/kg for 4-PeCDF. Thus, these PCDFs cause similar teratogenic insults to that previously observed for TCDD, but are approximately 1/10 to 1/100 times as potent. The interaction of any two furans with each other has also been investigated and appears to be additive in terms of induction of cleft palate. However, preliminary studies looking at biochemical indicators of toxicity in the same animals indicate that antagonistic interactions may also occur.

9. Disposition studies of 1-chloro-2-methylpropene (dimethylvinyl chloride-DMVC) and 3-chloro-2-methylpropene (CMP) showed that highest concentrations of radioactivity from either chemical administered by corn oil gavage were to be found in kidney, forestomach, and large intestine after six hours. The major CMP metabolite was identified as S-(2-methylpropenyl)-N-acetylcysteine. The major urinary metabolite from DMVC in male F344 rats was determined by its NMR spectra and synthesis to be 2-amino-4-thia-5-heptene-1,7-dioic acid. This metabolite is unusual in that the cysteine moiety is not acetylated as is the usual case in mercapturic acid derivatives. The unacetylated compound was also the major urinary metabolite in male B6C3F1 mice. The normal mercapturic acid, 2-acetamido-4-thia-5heptene-1,7-dioic acid, was also found in both male rats and mice, but in lower concentrations than the unacetylated metabolite. The mercapturic acid was identified by 1H nmr and from synthesis.

10. Absorption and metabolism of 5-(4-nitrophenyl)-2,4-pentadienal (NPPD)("Spydust"), a chemical allegedly used as a tracking agent in the Soviet Union, has been investigated in male F344 rats. The compound was readily absorbed by the gastrointestinal tract and rapidly excreted via the urine. NPPD was sparingly absorbed following dermal administration of 0.1, 1.0, and 10 mg/cm^2. The amount absorbed increased as the dose increased but the percent of the dose absorbed decreased as the dose increased. The material absorbed was rapidly excreted and the distribution and metabolism of the dermally administered compound was no different than from oral administration. A total of five metabolites, 4-nitrocinnamic acid, 4-acetamidobenzoic acid,

4-nitrohippuric acid, 4-acetamidocinnamic acid and 4-nitrobenzoic acid, were identified in urine by cochromatography with authentic standards and comparison of UV spectra. These metabolites result from some combination of oxidative metabolism of the pentadienal side chain, reduction of the nitro group, and conjugation of the resulting amino group with acetate or carboxylic acid with glycine.

11. An acute study of six chemicals reported to be forestomach carcinogens -- ethyl acrylate (EtAc), diglycidyl resorcinol ether (DGRE), 1,2-dibromoethane (DBE), 1,2-dibromo-3-chloropropane (DBCP), 1-chloro-2-methylpropene (dimethylvinyl chloride, DMVC), or 3-chloro-2-methylpropene(CMP), indicates that all six chemicals caused an increased incidence of forestomach mucosal cell proliferation and hyperkeratosis when administered for two weeks at doses reported to be carcinogenic. On the other hand, two chemicals, methyl methacrylate and dichloroethane, which were not carcinogenic in chronic studies, but are structural analogs of the forestomach carcinogens EtAc and DBE, respectively, had no significant proliferative effects on the forestomach mucosa when administered at comparable or higher doses than their carcinogenic analogs. These findings suggest that forestomach mucosal proliferation resulting from chronic gavage of selected chemicals may provide a favorable environment for tumor development.

12. Studies of the metabolism and distribution of halogenated dibenzofurans and dioxins are at the following stages of development:

a. Analysis of 2,3,7,8-tetrachlorodibenzofuran(TCDF) metabolites from rat bile has been initiated by preparing derivatized metabolites which will be analyzed by GC-MS.

b. 2,3,4,7,8-Pentachlorodibenzofuran (4-PeCDF) has been found in human tissues in Japan and Taiwan long after accidental poisonings. Its acute toxicity to guinea pigs is similar to TCDF. We are investigating its toxicokinetic properties in rats and monkeys. It is well absorbed (about 75% of the dose) after oral exposure in rats. No effect of dose was observed on absorption or excretion between 0.05-1.0 µmole/kg. Very little is detected in urine, and approximately 1%/day appears in the feces. The liver is the major depot, having 5-10 fold the concentration present in adipose tissue. Thus, 4-PeCDF appears to be very persistent with considerable potential for bioaccumulation.

13. Disposition studies of octachlorodibenzodioxin (OCDD) by different routes of exposure have indicated previously that OCDD seems to be poorly absorbed and metabolized. Repeated oral exposure results in a linear increase in the major tissue depots (liver, fat, skin). Based on elimination from liver, the biological half-life ($t_{1/2}$) is 4-8 months, suggesting that a two-year exposure in rats would never result in steady state levels. Thus, accumulation would continue. Further studies are in progress to determine if accumulation can result in alterations in hepatic chemical metabolizing activity.

14. Senescent changes in chemical metabolism have been investigated in an effort to better determine the fate of chemicals in animals used in chronic bioassays. These studies have produced the following results:

a) The absorption and excretion of compounds such as allyl isothiocyanate (AITC) (oil of mustard) and 4,4'-thiobis-6-t-butyl-m-cresol (TBBC) (a major rubber antioxidant) have been examined in old (~16 months) animals. These compounds are metabolized by different pathways and both qualitative and quantitative changes in metabolism will be assessed. The major metabolic pathway for AITC is conjugation with glutathione and the formation of a mercapturic acid (MA). The amount of mercapturic acid eliminated was constant, suggesting that older animals have the same ability to conjugate AITC with glutathione and form MA as do younger rats. TBBC is metabolized by conjugation with glucuronic acid. In fact, TBBC seems to be conjugated by the bilirubin-type of glucuronyl transferase and this activity shows an age-related decline. Our studies suggest that the decreasing level of the cofactor, UDPGA, per gram of tissue with age may limit the conjugation of TBBC.

b) Age-related changes in sensitivity to toxic effects of TBBC have also been studied. Rats of 3, 16, and 26 months were exposed to feed containing 0.5% TBBC for two weeks. There were few differences seen between the animals of different ages as to effects on weight, food consumption, pathology, or clinical chemistry values. There was a suggestion of a higher incidence, and greater severity, of leukemia in old TBBC-treated rats than old controls. This observation is being explored further.

c) Age-related changes in absorption of xenobiotics from the small intestine continued to be investigated using the technique of in situ luminal perfusion. The absorption of TCDD by animals of different age was examined by this procedure. The relative weight of the intestinal mucosa increases in the senescent rats. On a per mucosal weight basis, the absorption of TCDD decreases with increasing age. Further studies are in progress to elucidate this response.

15. Studies of the evolution of metallothionein-like proteins in nonmammalian species are being conducted to better understand the function of metallothionein (MT) in higher animals. Data obtained from studies of the scallop kidney taken in concert with ongoing amino acid sequence and structural studies of oyster cadmium binding protein suggest that one evolutionary pathway for MT may involve the insertion of cysteine based sequences into a more ordered protein with concomitant changes in structure and metal-binding site formation or gene cleavage with production of a smaller, more efficient molecule from a larger protein. In addition, studies focused on examining the role(s) of this protein in toxicity from multi-element exposure showed that its apparent induction by cadmium exposure ameliorated copper toxicity to the scallops but that this protective effect was associated with marked alterations of normal cytosolic metal-binding patterns for copper, zinc and cadmium.

16. Calcium channel blockers protect against chemically-induced gastric lesions. These studies were designed to investigate the effect of calcium channel blockers on chemically-induced gastric lesions in rats. Results of this study indicated that pretreatment of male F344 rats with the calcium channel blockers verapamil, diltiazem, or Mg^{++} significantly protected against ethanol-and indomethacin-induced gastric lesions as demonstrated by gross and histopathologic evaluation. Treatment of rats with calcium channel

blockers prior to ethanol or indomethacin resulted in a significant decline in the mean number of lesions per glandular stomach, the damaged area of the glandular stomach and the severity of lesions. Calcium channel blockers also caused a significant decline in the incidence of indomethacin-induced gastric lesions, but had no effect on the incidence of ethanol-induced gastric lesions. These results offer the first evidence that calcium channel blockers may play an important role in protection against chemically-induced gastric lesions and thereby offer insight into the mechanism of gastric ulcer formation.

17. The mechanisms of gallium arsenide (GaAs) toxicity are being investigated. These studies have examined effects of GaAs exposure on the heme biosynthetic pathway enzyme δ-aminolevulinic acid dehydratase (ALAD). Male CD rats received GaAs suspensions at doses of 50, 100 or 200 mg/kg via a single intratracheal instillation. At six days after treatment, liver and kidneys of GaAs-treated animals showed no changes in organ weight or evidence of cellular necrosis, but swelling of renal tubule cell mitochondria was observed. Lungs of GaAs-treated animals displayed marked necrosis and marked increases in lung weight/body weight ratios that were also observed in controls administered silica suspensions. Activity of ALAD in liver, kidney and blood was inhibited to 85, 65 and 20 percent of controls, respectively, at the 200 mg/kg dose level which was associated with a dose-related increase in urinary excretion of ALA. Measurement of heme precursors in urine coupled with assay of red blood cell ALAD activity may be of value as early biological indicators of GaAs toxicity.

18. Inhalation exposure of azodicarbonamide (ADA), a thermoplastic blowing agent and dough conditioner, was studied further in rats. The pattern of excretion after nose-only inhalation exposure was similar to that observed after oral exposure. This indicates that much of an inhaled dose is actually swallowed. Intratracheal administration resulted in 90% of the dose being excreted in the urine. ADA is rapidly metabolized to biurea. Essentially all the radioactivity in the urine and feces is biurea. Little ADA-derived radioactivity persists in the body three days after exposure. Thus, there is little likelihood that chronic exposure will lead to accumulation of ADA.

19. The disposition of inhaled 1,3-butadiene (BD), a chemical used in the manufacture of polymers, is being studied in male Sprague-Dawley rats and male $B6C3F_1$ mice to determine if species differences in disposition can explain species differences in the tumorigenic response to inhaled BD. BD can be separated from its metabolites using vapor line techniques. Both the mono- and di-epoxide can be detected in blood during BD exposure. Blood of mice contained 2-5 fold the concentration of epoxybutene than that of rats. At a given exposure concentration, mice retained more of the inhaled dose. Thus, species differences exist in the disposition and metabolism of inhaled BD that may in part explain the species differences in sensitivity.

20. The disposition of isoprene, a close structural analog of BD, is being studied in F344 rats. Mutagenic metabolites, 3,4-epoxy-2-methyl-1-butene and isoprene diepoxide, were detected in the blood of rats during exposure to isoprene and appeared to be exponentially related to the isoprene

concentration. The total amount of metabolites per dose decreased as the air concentration increased over the range of 8 to 8000 ppm. Adipose tissue may be a depot for isoprene. Urine was the major route of excretion of retained isoprene. These studies suggest that isoprene may have toxic properties similar to that for butadiene.

21. Disposition studies have begun on 1-chloro-2-propanol (CP), a compound used as an intermediate in the manufacture of propylene oxide. In F344 rats CP is completely absorbed after oral exposure and is rapidly metabolized. The major metabolite is $^{14}CO_2$ (60% of the dose), followed by urinary (30%) and fecal (5%) metabolites. We anticipate that some of the major urinary metabolites may be glutathione conjugates of CP. Inhalation studies are in progress.

22. Benzene has been shown to increase the incidence of tumor formation in Sprague-Dawley rats treated by the oral or inhalation route and in F344 rats and $B6C3F_1$ mice treated orally. The distribution of benzene and its metabolites in selected tissues is being studied in these three animal strains following an oral or inhalation route of exposure. Animals will be exposed to ^{3}H-benzene at 0.5 to 300 mg/kg/day (oral) or 1.0 to 300 ppm/6 hr/day (inhalation) for five days. Following the final exposure, animals will be sacrificed and benzene and its metabolites quantitated in urine, blood, feces, liver, lung, bone marrow, and Zymbals gland. Metabolites in oral cavity, stomach, skin around the mouth and skin on the back will be analyzed only at the low and high doses. Metabolites to be analyzed by HPLC include trihydroxy benzene, hydroquinone, catechol, phenol, muconic acid and water soluble conjugates as well as benzene.

23. Studies of the disposition of 1,3-dimethylol-4,5-dihydroxy-2-imidazolidinone (DMDHEU) indicate that it is eliminated almost completely unchanged in urine of male rats within 24 hours after a 50 mg/kg intravenous dose. DMDHEU was rapidly distributed to all tissues except adipose and brain, with highest concentrations located in the reproductive organs and urinary tract. Three days later, less than 0.5% of the dose remained in the animal, with highest concentrations again in the reproductive organs (as parent compound), bladder and adrenal glands. Oral absorption of DMDHEU increased from 17% to 38% of the dose as dose levels were increased from 500 to 2000 mg/kg. Dermal absorption from a non-occluded dose site was less than 6% of doses ranging from 0.3 to 13 mg/cm^2. Partial occlusion of the dose site resulted in more than a four-fold increase in absorption.

24. Hydrolytic cleavage of methyl-, ethyl- and butyl-glycol ether acetates has been studied in rat blood. In these studies it was observed that the rate of cleavage of glycol ether acetates to the corresponding glycol ethers by blood enzymes increases as the length of the alkyl chain, methoxy-, ethoxy- and butoxy increases. Half lives for these compounds at initial concentrations of 5 millimolar in blood at 37°C were 12.5, 9.5 and 3.4 min., respectively. Slightly longer half-lives (15.9, 12.6 and 5.3 min., respectively) were observed when initial concentrations of the xenobiotics in blood were 20 millimolar.

25. The disposition and metabolism of dual radiolabeled (^3H and ^{14}C) β-Bromo-β-nitrostyrene(BNS) is being studied in the rat following oral, dermal and intravenous administration. BNS has been shown to be hydrolytically cleaved to bromonitromethane and benzaldehyde. Approximately 20% of the carbon-14 in a 9 mg/kg intravenous dose of BNS was excreted in 72 hours as CO_2 and an equal amount as volatile, non-tritium containing organics. Slightly more than 25% of the dose of both carbon-14 and tritium was excreted as an apparent single metabolite (Y) in urine. Forty percent of the tritium was excreted in urine as a metabolite (Z) tentatively identified as hippuric acid. Approximately 12% of the dose of both carbon-14 and tritium was excreted in feces. Of the 8% of tritium and 13% of carbon-14 remaining in the animal, approximately two-thirds of the tritium and half of the carbon-14 were in blood. Ratios of tritium to carbon-14 in tissues were approximately unity at times less than one hour after dosing. The tritium to carbon-14 ratios then decreased with increasing time, indicating longer half-lives for metabolites formed from the side chain than for those formed from the aromatic ring. An exception to this was blood, where the tritium to carbon-14 ratio was still 0.85 72 hours after the dose was administered.

26. Metabolism and disposition of 1,1,1-Trichloroethane, commonly known as methylchloroform (MC), are being studied in rats and mice following exposure by gavage or inhalation. Results to date indicate that most of the dose is exhaled as the parent compound by both species; however, significant metabolism does occur and current efforts are directed to identification of metabolites, species related variations and mechanism of metabolism and toxicity involved.

27. The interactive effects of trichloroethylene (TCE) and chlorobenzene (CB) are being studied in vivo. TCE (700 mg/kg) has been shown to potentiate the hepatotoxicity of chlorobenzene (50 mg/kg) and alter the disposition and metabolic profile of CB. A greater percentage of a dose of CB (30% vs. 9%) was expired in the presence of TCE, with a corresponding decrease of excretion of ^{14}C-metabolites appearing in the urine. Interestingly, TCE decreased the urinary excretion of phenols/dihydrodiols, but increased the percent of urinary radioactivity present as mercapturic acid. These studies suggest that TCE-induced alterations in the disposition and biotransformation of CB could explain the enhanced toxicity of CB. Studies are underway to determine the no-effect dose of TCE with respect to alterations in the disposition of CB. Of the doses studied to date (200, 58, 5 mg/kg of TCE), it appears that 5 mg/kg reflects a no-effect dose on the disposition of 50 mg/kg of CB. A single dose of 5 mg/kg TCE does not potentiate the toxicity of CB. Studies are addressing the mechanism of this interaction.

28. Methylene-bis-thiocyanate (MbT) is being studied to determine the chemical and biological stability of this compound and its potential for degradation to cyanide. Initially, three doses of the compound will be administered orally and rates and routes of elimination determined. If dose does not affect the disposition of MbT, a non-toxic dose will be administered intravenously to determine the tissue distribution and elimination rates of MbT. Particular attention will be paid to the conversion of MbT to cyanide, a potentially toxic metabolite of MbT.

29. Studies of 1,2,4,5-tetrachlorobenzene (1,2,4,5-TCB) have shown a marked species difference between the dog and rat with respect to elimination of 1,2,4,5-TCB. The dog eliminates the compound more slowly than the rat (10% vs. 60% eliminated within three weeks, respectively). Studies with isolated hepatic microsomes suggest the species difference in rates of elimination is not a result of differences in rate of P-450 catalyzed hydroxylation of 1,2,4,5-TCB. Metabolites will be identified to determine if the metabolic profiles differ markedly. In addition, the rate of elimination of metabolites will be determined. One hypothesis is that the dog cannot conjugate a particular Phase I metabolite as readily as the rat. Because the 1,2,4,5-TCB may be a candidate for NTP chronic studies, a complete disposition study will be conducted for this compound in the rat.

30. In a study to determine its absorption and fate in higher animals ^{14}C-glyphosate has been administered orally by intubation to rats at doses of 5.6 and 56 mg/kg, doses that represent .001 and .01 times the LD_{50}. The major route of elimination of ^{14}C was in the feces with 75% and 55% of the 5.6 and 56 mg/kg doses being excreted within four days, respectively. At the 56 mg/kg dose, 34% of the dose was in the urine and for the lower dose, 19%. Less than 1% of either dose was found in the tissues at four days. The highest blood concentrations were 0.22% (at one hour) and 0.7% (at two hours) of the dose following the 5.6 and 56 mg/kg doses. Studies are also underway to determine if commercial formulations containing glyphosate (e.g., ROUNDUP) can enhance the absorption of ^{14}C glyphosate.

31. Studies of the absorption, metabolism and disposition of 2-hydroxy-4-methoxybenzophenone (HMB) indicate that gastrointestinal absorption of this compound is limited at high doses, but not at doses which humans are likely to encounter. Dermal absorption is appreciable when HMB is applied as an ethanolic solution or in a lotion. HMB is metabolized to at least five polar metabolites and excreted in urine and feces at the ratio of about two to one in favor of urine. The major metabolites are glucuronide conjugates of HMB and demethylated HMB plus other glucuronide and sulfate conjugates. Though dermal and gastrointestinal absorption were appreciable, there was no evidence that HMB is metabolized to a toxic or persistent metabolite and the parent compound is neither toxic nor persistent.

32. An investigation of the fate of N-(3-Chloroallyl)hexamininum chloride (CHC) was designed to determine if under biological conditions it is metabolized or degraded to release formaldehyde. Results of these studies indicate that CHC administered orally is excreted primarily in urine as various polar metabolites, secondarily in exhaled air and in trace amounts in feces. Only a trace, less than 0.12%, of the dose was detected in the exhaled air as formaldehyde. The remainder of the dose eliminated in exhaled air, accounting for approximately a third of the total dose, was in the form of CO_2. It is possible that a portion of this CO_2 represents the end result of formaldehyde metabolism, but this has not been confirmed.

33. A study of the gastrointestinal absorption and metabolism of D and C Yellow #11 (DCY) indicates that this compound is absorbed in a dose dependent manner with absorption limited to approximately 50% of the dose until the dose

manner with absorption limited to approximately 50% of the dose until the dose reaches approximately 4% of the diet at which point absorption decreases significantly. On absorption, DCY is readily metabolized and excreted primarily in bile and subsequently in feces. No intact DCY was detected in urine or feces. Neither DCY nor its metabolites persisted in tissues. These results indicate that DCY may be absorbed from drugs or cosmetics, but it is not likely to persist or bioaccumulate in tissues. These results do not establish the acute or chronic toxicity of DCY.

34. Studies of the fate of amsonic acid indicate that following administration by intravenous injection or in food at concentrations up to 5% in the diet that gastrointestinal absorption of this compound is dose dependent and at the higher doses absorption may be as low as 1% of the dose. The intravenous dose was readily excreted in urine, and examination of the tissues indicates that amsonic acid is not retained. These results indicate that any observations of chronic toxicity made in the course of study of this compound should be analyzed with due consideration of its poor absorption. That is, the lower doses to which humans would likely be exposed most probably will be more completely absorbed than those high doses used in the animal studies of chronic toxicity.

35. Ongoing studies of N-phenyl-2-naphthylamine are designed to determine if this compound is metabolized or otherwise degraded to the known carcinogen 2-naphthylamine, as previously reported by other investigators. Using a sensitive gas chromatography technique to analyze metabolic products excreted in urine, the previously reported route of excretion for 2-naphthylamine, it has not been possible to detect the presence of the carcinogenic metabolite or its metabolites. This work is continuing, but if these results hold true, they will indicate that any observed chronic toxicity observed with this compound must be attributed to the parent molecule or 2-naphthylamine present as a contaminant of the technical product used rather than the suspected carcinogenic metabolite. Previous reports of the formation of 2-naphthylamine as a metabolite may have resulted from the use of contaminated starting material.

36. Methods to assess human metabolism of chemical xenobiotics are being developed to aid in extrapolation of toxicity testing results. Achievements in this area include the following.

a. Metabolism has been assessed in isolated hepatocytes, hepatic S-9 fraction, liver slices and kidney microsomes.

b. Comparative metabolism of benzo(a)pyrene by rat and human hepatocytes indicate that metabolizing activity is 2-3 times higher in rat than human hepatocytes.

c. Metabolism of benzidine, caffeine and trichloroethylene by human hepatocytes is variable, being low for benzidine and caffeine, but high for trichloroethylene.

d. The metabolizing activity of human kidney tissue is surprisingly low when compared to the rat liver.

e. Efforts are continuing to develop improved assays for metabolizing activity and maintain this activity for extended periods by cryopreservation.

FY 1987 PROGRAM PLANS

Ongoing studies of chemical disposition and metabolism will be completed. New chemical disposition studies will be initiated as requested by NTP or intramural personnel. Studies of mechanisms of chemical metabolism, toxicity and teratogenicity will be continued as will efforts to assess human metabolism of chemical xenobiotics. These studies will include *in vivo* and *in vitro* assays for interactive toxicity, investigations of age, species, sex and dose related toxicity and investigations of chemical and biochemical parameters which determine absorption, distribution, metabolism and excretion of chemicals. (CONTACT PERSON: Dr. H.B. Matthews)

NIOSH

FY 1986 ACCOMPLISHMENTS

Biological Monitoring -- Two manuscripts have been published and three accepted for publication on biological monitoring methods and their application to assessment of workplace exposures. A high pressure liquid chromatography (HPLC) method for measuring 4,4'-methylenebis (orthochloroaniline) (MBOCA) in urine was validated in the laboratory. This assay will be used for assessing dermal absorption of MBOCA. Methods were developed and applied to the monitoring of workers exposed to cytotoxic drugs. (CONTACT PERSON: Dr. L. Lowry)

Blood and urine samples were obtained from human subjects exposed to vapors of methyl ethyl ketone (MEK), acetone or a mixture of the two. Blood samples were assayed for the parent compounds by headspace gas chromatography. Methods for the assessment of MEK metabolites in urine are being developed and will be used for the analysis of urine samples. (CONTACT PERSON: Mr. F. Phipps)

A method for measuring the urine concentration of 2-ethoxyacetic acid, the major metabolite of 2-ethoxyethanol (2-EE), was developed and used to assess exposure of shipyard painters to 2-EE. A preliminary method was developed to assess human dermal exposure to the insect repellent m-N,N'-diethyltoluamide (m-DET) by measurement of m-DET in urine. Two metabolites of m-DET, m-toluamide and m-N-methyltoluamide, were identified in the urine of humans and rats exposed to m-DET. (CONTACT PERSON: Mr. A. W. Smallwood)

A biological monitoring method for assessing worker exposure to coal tar pitch was developed and validated using urine from rats dosed with a polycyclic aromatic hydrocarbon (PAH) marker, pyrene. The metabolite of pyrene, 1-hydroxypyrene, was identified by GC-MS and quantitated in rat urine using HPLC with fluorescence detection. 1-Hydroxypyrene was detected in the urine of smokers, while only trace amounts were found in the urine of non-smokers. (CONTACT PERSON: Mr. W. Tolos)

FY 1987 PROGRAM PLANS

Biological Monitoring -- The field evaluation of the newly validated method for MBOCA in urine will be conducted on workers exposed to MBOCA. Worker exposure to glycol ether acetates will be assessed using the newly validated method for measuring glycol ether acid metabolites in urine. A report on the relationship of glycol ether exposure and urinary glycol ether acid metabolites will be submitted for publication. A method to assess human exposure to carbon disulfide by measurement of the metabolite 2-thiothiazolidine carboxylic acid (TTCA) will be applied to workers exposed to carbon disulfide. (CONTACT PERSON: Dr. L. Lowry)

Methods for MEK metabolites in urine will be applied to the assessment of human volunteers previously exposed to MEK. Headspace gas chromatography methods will be developed for simultaneous determination of methyl isobutyl ketone (MIBK), acetone and ethanol in blood of humans exposed to these solvents, either in pure form or in mixtures. (CONTACT PERSON: Mr. F. Phipps)

Methods for measuring m-DET in blood and urine of human volunteers will be completed. Pilot studies will be performed to assess the dermal absorption of various commercial formulations of m-DET under a variety of conditions of application site, temperature and humidity, and evaporation. Outcome of this work will indicate the feasibility of using blood or urine to monitor dermal absorption of m-DET. (CONTACT PERSON: Mr. W. Smallwood)

Worker exposure to coal tar pitch will be assessed by measuring 1-hydroxyprene in urine. Coke oven workers, who have the highest potential for exposure, will be monitored for both 1-hydroxypyrene in urine and PAHs in their working environment. Results of the two monitoring programs will be compared. (CONTACT PERSON: Mr. W. Tolos)

Animal studies will be utilized to develop HPLC or GC techniques for detection of hemoglobin or DNA-adducts following exposure to aromatic amines. MBOCA will be used as a model compound. The formation of macromolecular adducts and urinary metabolites of MBOCA will be evaluated for use in biomonitoring. (CONTACT PERSON: Mr. K. Cheever)

NCTR

FY 1986 ACCOMPLISHMENTS

Gentian Violet

The avian and mammalian dye metabolites of gentian violet (GV) were tested for mutagenicity in both the Ames plate assay with *Salmonella typhimurium*, and in continuous culture with *Escherichia coli* WP2s. The toxicity of GV to *S. typhimurium* at a concentration as low as 10 mg/plate was confirmed and extended to its demethylated metabolites. The results make this system of little use for dye testing. However, a structure-activity relationship was found among GV, pentamethylpararosaniline (PMR), N,N,N',N'-tetramethylpararosaniline (dTMR) and N,N,N',N"-tetramethylparaosaniline (tTMR) in the mutagenic response of *E. coli* in continuous (chemostat) culture. Response varied inversely with the degree of methylation of the pararosaniline backbone with GV causing 32 mutants/10^8 generation and tTMR causing 135/10^3 generation.

Chromatographic analysis indicates that GV and PMR are reduced in the chemostat cultures to leuco GV and leuco PMR. These metabolites, found also in mammalian tissues, are mutagenic to *S. typhimurium* in the Ames plate assay with S9 activation.

Sulfamethazine

The residue study in Fischer 344 rats and $B6C3F_1$ mice was begun. All animals are being dosed three times daily for seven days by gavage with an aqueous solution of ^{14}C-sulfamethazine (^{14}C-SMZ) in an amount equivalent to that which rats or mice on the chronic toxicity assays would consume in feed at the 300 ppm level. Total residues of ^{14}C-SMZ in liver, kidney, gonad, muscle, and fat are being measured by combustion analysis. Residue levels decrease from a high in liver (9.38 ppm, male) to a low in fat (0.80 ppm, male). Values for female rats are similar.

HPLC of extracts of male rat tissues show the presence of seven metabolites with SMZ and acetyl SMZ predominating in liver and kidney. SMA and acetyl SMZ alone are found as excreted metabolites in urine from female rats while two additional metabolites are detected in urine from male rats.

FY 1987 PROGRAM PLANS

Gentian violet -- It is anticipated that final reports for residue studies in rats and mice will be on file.

Sulfamethazine -- It is anticipated that final reports for residue studies in rats and mice will be on file. (Contact Person: Dr. N. A. Littlefield)

CHEMICAL PATHOLOGY

NIEHS

The Chemical Pathology Branch functions to improve the understanding of the nature of chemically induced lesions in rodents and to standardize the diagnosis, documentation and interpretation of these lesions. The Branch devotes a major share of its efforts to reviewing pathology data and histological diagnoses from studies conducted for the National Toxicology Program (NTP). The Branch is also responsible for the production, health status, and genetic integrity of the rodents used in the NTP. In addition, the Branch conducts in-house studies and studies under contract, aimed at elucidating the nature and significance of pathological changes found in rodents. These efforts support the NTP mission to define the toxicity of chemicals of environmental concern. The Branch is composed of five integrated Sections: Tumor Pathology, Toxicologic Pathology, Experimental Pathology, Laboratory Animal Medicine, and Histology and Electron Microscopy.

Tumor Pathology Section

The Tumor Pathology Section assures that the pathology evaluations of the chronic NTP animal studies are precise, accurate, and state-of-the-art. The major emphasis in the past year has been on improving the quality of the pathology data that are produced for NTP studies.

Increased effort continues to assure that both tumor and non-tumor diagnoses in the two-year studies are consistent and complete. This is especially important in detecting increased incidence or severity of a naturally occurring lesion. In the past two years, data validation steps have been strengthened and rearranged to assure better pathology data and a more orderly data flow. The initial pre-quality assessment (QA) data review occurs at a time when slide, blocks, and wet tissue are at the contract laboratory and inconsistencies found can be easily corrected. Following approval, all material is shipped to the Archives where slide/block match-up, animal identification, and check for untrimmed lesions occur. This assures that all lesions have been addressed before the study proceeds to pathology quality assessment. The study pathologist is now included in the Pathology Working Group (PWG) review, and spends one day prior to the PWG reviewing discrepancies and treatment-related changes. Since many minor disagreements are resolved, the PWG can focus on significant treatment-related effects plus unresolved discrepancies. Data clerks update pathology diagnoses during this two-day procedure and at the end of the PWG the study pathologist confirms the updates and signs the tables which are now ready for computer entry. This has resulted in better dialogue between contract and NTP pathologists, better utilization of PWG expertise, and generation of final pathology tables two to three months earlier.

FY 1986 ACCOMPLISHMENTS

Chronic Pathology Studies Reviewed -- During FY 1986, pathology reviews of 46 chronic studies were held (Table 18). An important goal was to improve the pathology data evaluation and to do this in a manner that would save time and money. To accomplish this, a pre-QA data review was instituted. The pathology data from the laboratories are now reviewed prior to submission of the slides for histological review. If data duplication or inappropriate terminology are found, the data and the review results are returned to the laboratory for corrections. This has placed the responsibility for producing quality data upon the laboratory and has resulted in submission of better quality data in subsequent studies.

A second change to save time and money was the elimination of the review of random animals from the intermediate dose animals during pathology quality assessment. This saves approximately twenty percent in time and man-hours on the QA contract for each study completed. This neither jeopardizes study results, since all target tissues are reviewed, nor historical data, since all tumors in controls are reviewed.

A third change was to have the study pathologist present the day prior to the Pathology Working Group (PWG). The study pathologist reviews the QA and PWG chairperson's diagnoses and makes appropriate updates in the data prior to the PWG. This saves the PWG from reviewing cases that the study pathologist clearly agrees need to be changed. This has allowed the PWGs to devote more time to examining the treatment-related changes and the controversial lesions. These management changes are resulting in better quality data in the NTP technical reports without costing additional time or money. (CONTACT PERSON: Dr. S. L. Eustis)

Pathology Data Audits -- The raw data from each completed study continues to be reviewed by an audit team consisting of toxicologists, chemists, and pathologists. The audit team is composed of NTP and contract personnel. The audit report is reviewed by NTP pathologists and other staff before a final Technical Report is issued. Audits created the awareness that some gross lesions were being missed either at time of necropsy or during the trimming of the tissues. Thus, an NTP pathologist or representative is present at the first day of terminal sacrifice for all two-year studies. This has resulted in better accountability for gross lesions. (CONTACT PERSON: Dr. S.L. Eustis)

Proliferative Pancreatic Lesions in F344 Rats -- Proliferative exocrine pancreatic lesions are more common in rats receiving corn oil as a vehicle during gavage studies than in untreated controls. The nature of this lesion continues to be explored through cooperative agreements with Dartmouth Medical School, Northwestern Medical School, and the University of Missouri.

The Dartmouth Medical School task objectives are to evaluate the significance of the increased incidence of proliferative acinar lesions and their relationship to dietary oil. Specifically, gavage oil versus dietary oil (bolus effect), Lewis rat vs. F344 rat response, growth potential of induced pancreatic lesions (cell culture and transplantation), presence of cellular oncogenes and role of dietary oil as a promotor or initiator of pancreatic lesions will be evaluated. Results have indicated that the amount of oil is more important than whether the oil is given in diet or by gavage. These studies will have relevance to the NTP during the evaluation of chemical carcinogenicity studies in which corn oil is the vehicle, and, more generally, to investigators involved in defining the relationship between nutrition and cancer.

The Northwestern Medical School group is studying the effect of short-term and long-term administration of vegetable oils on DNA synthesis and mitosis of acinar cells and on the induction of proliferative acinar cell lesions, investigating the promoting effect of vegetable oils on 4-hydroxyquinoline and ciprofibrate initiated pancreatic lesions, and elucidating the biological properties of the acinar cell lesions induced by long-term administration of vegetable oils. These studies will aid in the understanding of the initiation and promotion of pancreatic cancer which is a considerable cause of death in man. These studies will also have relevance to rodent nutrition and toxicology studies where oil is used as a vehicle.

Investigators at the University of Missouri are aimed at determining the role of pancreatic trophic hormones in vegetable oil induced pancreatic proliferations. So far these studies suggest that the secretion of cholecystokinin is not stimulated substantially by the administration of corn oil. (CONTACT PERSON: Dr. G.A. Boorman)

Pathology Support for the NTP - Quality Assurance -- Pathology data are subjected to a thorough pathology quality assessment through a contract with Experimental Pathology Laboratories. The objectives of the contract are (1) to provide pathology quality assessment of all NTP studies, (2) provide pathology training to contract laboratory pathologists, and (3) photograph lesions for NTP pathologists and toxicologists who participate in pathology working groups, seminars, and workshops. (CONTACT PERSON: Dr. G.A. Boorman)

Management of the NTP Archives -- During the past 15 years, the National Cancer Institute and the National Toxicology Program (NTP) have conducted over 300 two-year studies (often proceeded by 90-day toxicology studies) in rats and mice. The slides, blocks, and wet tissues from these studies are archived for retrospective study and evaluation by the NTP and other interested scientists. Objectives of the NTP Pathology Archives contract are to maintain this resource in a dynamic "user friendly" basis. In addition, all new studies are inventoried, slide/block match-ups are performed, and wet tissues are checked for correct label, presence of untrimmed lesions and presence of correct animal identification. The NTP Archives personnel provide answers to questions that arise during the preparation of technical reports. They provide black and white plus color photographs of selected lesions for NTP pathologists and chemical managers. The Archives personnel trim in lesions identified during audits and provide pathology data coordination.

The NTP Archives, located in Research Triangle Park, NC, are a unique national resource of over 5.5 million histological slides of spontaneous and induced lesions in rats and mice. The data is maintained in an access limited protected environment and is computerized for easy data access. This resource can be used for retrospective studies, to verify completed studies and to access and review new studies in an orderly manner. Interested scientists can review pathology data from studies after receiving permission from the Chemical Pathology Branch Chief. The Archives are now in the process of identifying old studies where the wet tissues may be discarded. The studies are announced in the Federal Register and a 30-day comment period is allowed prior to discarding tissues. Since the slides, blocks and paper data are being saved, this will result in savings without jeopardizing the integrity of the study. For more information or scheduling of user facilities, contact Dr. G.A. Boorman, Chief, Chemical Pathology Branch, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709; or call (919) 541-3231 (commercial), or 629-3231 (FTS).

Forestomach Lesions in Rats -- The nature of forestomach lesions in rats is being evaluated by exposing rats to methyl bromide by gavage in peanut oil. Methyl bromide, a widely used fumigant and known irritant, was reported to cause forestomach carcinomas in rats by gavage. There is continuing concern about the role of irritation in cancer development.

Forestomach lesions were not found in control rats receiving peanut oil only for 13 or 25 weeks while at 13 weeks forestomachs from rats exposed to methyl bromide were contracted and adherent to the liver and spleen. Inflammation, acanthosis, fibrosis and marked pseudoepitheliomatous hyperplasia were found microscopically in forestomachs from treated animals. Evidence of malignancy was seen in one rat treated with methyl bromide for 25 weeks. Methyl bromide-induced hyperplastic lesions of the forestomach regressed when treatment was discontinued. This finding suggests that the induction of forestomach carcinoma is both time and dose dependent, and highlights the need for regression experiments to better define the nature of complex forestomach lesions in rodents, especially when resulting from an irritating chemical given by gavage. These results were accepted for publication in 1986. (CONTACT PERSON: Dr. G.A. Boorman)

Myelotoxicity/Immunotoxicology -- In collaboration with the scientific staff of the Immunotoxicology Section of the Systemic Toxicology Branch, the Tumor Pathology Section provided pathology support and myelotoxicity evaluation for several mouse studies as follows:

(1) Ethylene glycol (EG) or ethylene glycol monomethyl ether (EGMME) was administered to both sexes of mice by gavage for four consecutive days. EGMME is more toxic than EG to the hematopoietic system in B6C3F1 mice. Female mice became anemic and males showed leukopenia and testicular atrophy following EGMME exposure.

(2) Studies which were performed to determine if there was residual marrow effect in B6C3F1 mice which were sublethally irradiated 15 weeks after EGMME exposure showed that EGMME results in a significant residual marrow damage in mice, as assessed by the colony formation assay, at a time when marrow cellularity and peripheral blood counts have apparently totally recovered from irradiation.

(3) Effects on bone marrow parameters of a four-day inhalation exposure to methyl isocyanate (MIC) in female mice were examined. MIC exposure was associated with myelotoxicity as evidenced by hypocellularity, suppression of pluripotent stem cells (CFU-S), granulocyte macrophage progenitors (CFU-GM) and erythroid precursors (CFU-F) in both dose groups. MIC exposure acutely causes cell death of lining epithelium of the nasal passages and major airways with transient alterations of bone marrow parameters that are likely related to

the pulmonary injury either directly or secondarily through thymic atrophy. Lack of myelotoxic effects one year post exposure support the hypothesis that the bone marrow alterations are secondary to acute pulmonary injury. (CONTACT PERSON: Dr. G.A. Boorman)

Toxicologic Pathology Section

The Toxicologic Pathology Section assures the quality of anatomic pathology from acute, prechronic and interim sacrifice studies in mice and rats, establishes diagnostic nomenclature for toxicologic pathology, defines organ specific toxic lesions and correlates treatment-related toxic lesions in target organs with neoplasia in the same organs in chronic toxicologic studies. Cross-study comparison allows correlation of target organs with the chemical structure of the test compound. Attempts are made to identify preneoplastic lesions and study the biologic behavior of toxic induced proliferative lesions.

FY 1986 ACCOMPLISHMENTS

Prechronic Pathology Studies Reviewed -- During FY 1986, 14 prechronic studies were reviewed by the Toxicologic Pathology Section. Studies are evaluated for quality of histotechnique, tissue counts, slide inventory, accuracy and completeness of diagnoses. Review of the study includes six randomly selected animals sacrificed at the termination of the study from the highest dose groups with at least six survivors and six randomly selected controls from each sex. All slides are reviewed from animals that are moribund sacrificed or die prior to termination of the study. All identified target organs are reviewed in all subsequent lower doses until a no-effect level is established. All tumors are reviewed. These findings are reviewed by the Section Head, and a Pathology Working Group (PWG) chairperson is designated. The PWG process has been described previously (FY 1986 Annual Plan, p. 152). This extensive review of prechronic toxicologic studies has resulted in a better understanding of chemically induced lesions in the host, target organ interactions, and has established a baseline for spontaneously occurring lesions in 19- to 22-week old Fischer rats and B6C3F1 mice. More emphasis has been put on definition and classification of nonneoplastic toxic lesions. NTP analysis of these studies has also provided a mechanism for monitoring contract laboratory work performance. (CONTACT PERSON: Dr. M.R. Elwell)

Pathology Review of Interim Sacrifice Studies -- During FY 1986, the pathology in four interim sacrifice studies was reviewed by the Toxicologic Pathology Section (Table 19). The majority of NTP chronic toxicologic studies have a 15-month interim sacrifice designed into the protocol. The goal is to identify and study chronic treatment-related toxic disease, before these lesions are masked by spontaneous or chemically induced neoplastic disease. In many cases, multiple interim sacrifices at 6, 12, 18 or 6, 9, and 15 months, respectively, are implemented in the chronic experimental design to study the pathogenesis of toxic disease in the host. Stop studies where the chemical is given for 13 weeks and treatment discontinued are occasionally used to determine if a specific toxic lesion is reversible or progresssive over the balance of the 24-month chronic study. (CONTACT PERSON: Dr. M.R. Elwell)

Toxicology Data Management System (TDMS) -- The NTP currently has all ongoing chronic toxicity studies on the TDMS computer system. This represents ten NTP contract laboratories and three interagency agreement sites. Data collection methods are adequate, but microprocessor hardware is reaching its lifespan. The NTP has taken the initiative to replace TDMS with a more state-of-the-art, non-hardware dependent computer system. The Pathology Code Table (PCT) developed for TDMS will be implemented in the replacement system to maintain continuity and standardization of the NTP pathology database. (CONTACT PERSON: Dr. S.L. Eustis)

Special Pathology Laboratory -- The Chemical Pathology Branch has developed the capability to use immunohistochemical stains such as immunoperoxidase and immunogold to identify tissue antigens on various tumors. One example in this regard is the demonstration of laminin in yolk sac tumors in mice. This staining conclusively demonstrated the nature of the tumor, a conclusion that could not be reached by morphological evidence alone. It is planned to explore the use of this technique to demonstrate the presence of oncogenes in tumor tissues. (CONTACT PERSON: (Dr. G.A. Boorman)

Experimental Pathology Section

The Experimental Pathology Section develops and validates animal models for chemical toxicity and carcinogenicity, investigates the pathogenesis of lesions observed in toxicity and carcinogenicity studies, investigates mechanisms of carcinogenesis, applies new diagnostic tools for anatomic pathology, and develops and standardizes clinical pathology procedures for use in rodent studies.

FY 1986 ACCOMPLISHMENTS

Short-term Rat Liver Tumor Model Studies -- Three contracts were awarded to refine the Peraino (one-day-old rat) or Pitot liver tumor models. Once refined, these models will be utilized to assess the relative initiating and promoting activities of rodent hepatocarcinogens. Model refinement took place during FYs 1983, 1984, and 1985 and included definition of dose response to several initiators and promotors, comparison of standard versus purified diet on liver tumor response, determination of sex differences in responsiveness of model, comparison of different routes of chemical administration on response, and characterization of potential indicators of neoplasia (histochemically altered foci) in the livers of treated rats. Testing of chemicals in the refined model commenced in March 1986. (CONTACT PERSON: Dr. R.R. Maronpot)

Strain A Mouse Pulmonary Tumor Validation Study -- The strain A mouse pulmonary tumor bioassay system was used to test 60 chemicals to determine how results of this short-term bioassay compared with results of rat and/or mouse conventional two-year carcinogenicity studies. The preliminary conclusion that the strain A mouse test system would not identify most of the chemicals found carcinogenic in the conventional two-year studies was confirmed. Further comparisons of strain A test results with organ-specific carcinogenic responses in the two-year studies and with genotoxicity test results were made late in FY 1983. A manuscript summarizing results of this effort has been submitted for publication. (CONTACT PERSON: Dr. R.R. Maronpot)

Clinical Pathology Studies -- Clinical pathology has been used for the past ten years to varying degrees to help evaluate potential toxicity of chemicals undergoing 90-day and two-year studies. Yet, the utility and the cost effectiveness of the clinical pathology studies have not been thoroughly reviewed. Government and industry pathologists are reviewing past NTP experience and will recommend the best options for the future. (CONTACT PERSON: Dr. M.B. Thompson)

In Vivo Nuclear Magnetic Imaging and Spectroscopy on Rodents -- Rats treated with chemicals that produce specific organ damage or tumors are currently being studied by NMR imaging in collaboration with Duke University. Advances were made during the past year in animal handling and in the acquisition, reconstruction and storage of magnetic resonance (MR) data will make possible experiments that are technically and experimentally complex. During the past year an extensive series of MR images of the normal rat brain and of the live chick embryo were made. Anatomic detail approaching microscopic resolution was produced. Additionally, spontaneous pituitary neoplasms, one as small as 1.5 mm in diameter, were readily detected in untreated rats that were two years old. Also, images of the liver made during 1986 were superior to those produced a year earlier. A long-term initiation-promotion study, designed to evaluate the formation, growth and regression of hepatic neoplasms in rats began in May 1986. Images will be made three days a week for approximately one year. This study will help define the role of MR imaging in carcinogenesis studies. Four manuscripts have been submitted for publication and one has been published. (CONTACT PERSON: Dr. M.B. Thompson)

Study of Chemically Induced and Spontaneous Tumors for Oncogene Activity -- The Branch, in collaboration with Dr. Marshall Anderson of the Biometry and Risk Assessment Program, has been studying the activation of oncogenes in spontaneous and chemically induced tumors in rats and mice. In rats activated oncogenes have been identified in chemically induced but not in spontaneous neoplasms. In mice the pattern of oncogene activation is different in spontaneous versus induced tumors. This research holds promise for increasing our understanding of induced tumors in rodents. (CONTACT PERSON: Dr. R.R. Maronpot)

Laboratory Animal Management

The Laboratory Animal Management Section provides genetically defined rodents of known microbial status for NTP toxicology and carcinogenesis studies. The rodent production program is designed to assure the timely supply of high quality, disease free rats and mice for toxicologic and carcinogenic evaluation of chemicals. The production of quality animals is a cooperative effort between the rodent production facilities and the NTP.

Two rodent production facilities are currently under contract to provide a specified number of F-344 rats and B6C3F1 mice at weekly intervals for NTP toxicology and carcinogenesis studies. Microbial monitoring continues to be the priority for animal management to maintain the quality of the animals supplied to the NTP supported studies. Two diagnostic laboratories under contract conduct disease monitoring of the rodent production facilities at monthly intervals. The sentinel animal program of the prechronic and chronic toxicity and carcinogenicity studies continues to serve as the monitoring program for viral infections in each animal room at the toxicology testing laboratories. Genetic integrity of the production and test rodents is monitored by periodic evaluation of retired breeders and weanlings of the production colonies as well as weanlings supplied to the testing facilities.

FY 1986 ACCOMPLISHMENTS

The rodent production is being modulated to provide an adequate number of animals to all new study starts and to decrease any excess production. This procedure resulted in decrease of rodent production to approximately 80% of the FY 1985 level, while maintaining and improving the quality of animals. New centralized rodent foundation colonies of C57BL/6N and C3H/HeN MTV^- mice and F-344/N rats with pedigreed stock from the NIH repository were started under contract. This project is providing better control over the genetic integrity of the expansion stock for new rodent production centers. Two new rodent production centers started production of rodents for toxicology studies. A new genetic monitoring contract was started in FY 1986 to determine the genetic integrity of the inbred mice, rats and hamsters.

Utilizing the reports on the frequency of viral infections by laboratory and by animal room of the sentinel animal data file, programs and procedures were developed to reduce or eliminate the viral infections of animals in subchronic and chronic studies. All but two subchronic and chronic toxicity and carcinogenicity studies started since June 1985 are free of viral infections. The utero-ovarian infections and peritonitis of female mice in the chronic studies were controlled by implementing additional sanitization procedures and terminating the rodent production colonies harboring the organisms associated with these infections.

A workshop was held in October 1985 to "Optimize Diet for Rodents in Chemical Carcinogenicity Studies" with participants from food, chemical and pharmaceutical industries, rodent diet manufacturers, regulatory agencies and experts from research institutes including universities and the National Institutes of Health. In this workshop ingredients, composition and contaminants of rodent diets for chemical carcinogenicity studies were discussed.

Two projects to improve the current mouse feeders and to evaluate feeders with innovative design are in progress. The purpose of these projects is to develop a mouse feeder to decrease the feed spillage and to increase the accuracy of feed consumption and compound consumption measurements.

FY 1987 PROGRAM PLANS

1. Widely disseminate, discuss and publish the results of the workshop on "Strains of Mice for Chemical Carcinogenicity Studies." Develop programs and protocols to evaluate strains of mice, especially hybrid strains (other than B6C3F1) to determine their suitability for chemical carcinogenicity studies.

2. Widely discuss and publish the results of the workshop to "Optimize Diet for Rodents in Chemical Carcinogenicity Studies." Develop programs and protocols to evaluate different diets to determine their suitability for chemical toxicity and carcinogenicity studies.

3. Refine the programs and procedures to reduce or eliminate the microbial infections of animals in the chemical toxicity and carcinogenicity studies.

4. Further evaluate improved and new mouse feeders for their suitability to provide accurate feed and compound consumption measurements in chemical toxicity and carcinogenicity studies.

5. Evaluate the effect of irradiation on the nutrient and microbial content of the rodent diet. Assess the need and determine the suitability of irradiated diet for chemical toxicity and carcinogenicity studies.

These plans extend the overall goal of the Laboratory Animal Management programs to determine the suitability of different rodent models for chemical carcinogenicity studies, to produce sufficient numbers of these rodents in a genetically defined and disease free state, to assist the toxicology testing laboratories to maintain the animals on studies free of diseases, and to improve the animal care equipment and supplies. (CONTACT PERSON: Dr. G.N. Rao)

Histology and Electron Microscopy Section

The Histology and Electron Microscopy Section is primarily a support facility serving the NIEHS Intramural Research Program (60%) and Toxicology Research and Testing Program (40%). The histology laboratory provides basic cutting and staining services and has limited capability for special stains and techniques. The electron microscopy laboratory also provides routine cutting and staining services. In addition, it provides technical help in the use of electron microscopy and interpretation of these observations.

FY 1986 ACCOMPLISHMENTS

During FY 1986 the histology laboratory supported 45 NIEHS scientists. In pursuing this effort, the laboratory sectioned and stained a total of 32,000 blocks of tissues. The electron microscopy laboratory supported 22 NIEHS scientists in their needs for ultrastructural examination of animal materials. (CONTACT PERSON: Mr. F.A. Talley)

OTHER FY 1986 CHEMICAL PATHOLOGY BRANCH ACCOMPLISHMENTS

Classification Scheme for Rat Liver Tumors -- The Branch devotes considerable effort to understanding rodent lesions and developing criteria that reflect this understanding. A notable landmark in this regard is the publication of a classification scheme for rat liver tumors. For the past ten years, the term "neoplastic nodule" has been used to designate a lesion that may represent hyperplasia or a benign tumor. While a single term brought uniformity to classification of rat liver neoplasia, there has been considerable controversy for using a term that has different meaning to different pathologists. The Chemical Pathology Branch has reviewed numerous studies where the rat liver was the target organ and has gained more understanding on the type and nature of lesions found in the rat liver.

Dr. Maronpot collected a study set of problematic rat liver lesions for review by a number of pathologists. A classification scheme was devised using standard pathological terminology for use by these pathologists to classify the lesions. The proposed scheme and manuscript was widely reviewed and received considerable support prior to publication. We feel that this publication represents a significant progression in the classification of rat liver tumors.

The Branch continues to use the rat liver models both in-house and through contract studies to augment our understanding of the rat liver tumors. These studies proved useful in our development of a classification scheme. The studies to date would suggest that the F344 rat is not overly sensitive to hepatocarcinogens and may be less sensitive than the Sprague-Dawley rat.

Pathological Evaluation of Methyl Isocyanate in Rodents -- The Chemical Pathology Branch provides support for NIEHS and NTP investigators. We have recently completed the pathology evaluation of rats and mice that were exposed to methyl isocyanate. The principal investigator for this study was Dr. John Bucher of the Carcinogenesis and Toxicology Evaluation Branch. Nearly one thousand animals were subjected to a histopathological evaluation which revealed that the lesions were confined to the respiratory tract and were characterized by necrosis and loss of the lining epithelium of the nasal passages and the airways. There was rapid regeneration but in the major bronchi in mice and in several generations of bronchi and bronchioles in rats, there was intraluminal fibrosis. The fibrotic lesions appeared to resolve slowly and were still present at the end of the 90-day study.

In addition, an ultrastructural evaluation was completed for the nasal passages of the male rats and mice which showed that there was regeneration of the complex olfactory epithelium in the nasal passages that appeared to originate from cells of the Bowman's glands. This study provides additional information on olfactory epithelial regeneration which has been difficult to study because of a lack of a suitable model. Methyl isocyanate provided a useful model in that it caused complete loss of epithelium while leaving the underlying tissue intact.

FY 1987 CHEMICAL PATHOLOGY BRANCH PROGRAM PLANS

Pathology Review and Workshop Activities -- In FY 1987 Quality Assurance and PWG functions will be continued for two-year studies to maintain a uniformly high quality of pathology for the Program. This will continue at FY 1986 levels or higher to shorten the time lag between the end of the study and the generation of the final pathology tables. To save time and money, PWGs will be held for prechronic and interim sacrifice studies on an as needed basis. The study pathologist will continue to participate in the PWG process.

Interlaboratory Variability in the Diagnosis of Neoplasms -- During FY 1987 investigations will continue to determine the cause of significant variability in the incidence of certain neoplasms among different contract laboratories. (CONTACT PERSON: Dr. G.A. Boorman)

Special Pathology Techniques -- The Chemical Pathology Branch has developed in-house capability to use immunohistochemical stains such as immunoperoxidase and immunogold to identify tissue antigens on various tumors. It is planned to explore the use of this technique to demonstrate the presence of oncogenes in tumor tissues. (CONTACT PERSON: Dr. G.A. Boorman)

TABLE 18
PATHOLOGY DATA REVIEWS DURING FY 1986

CHEMICAL NAME	CAS NO.	SPECIES
Allyl Glycidyl Ether	106-92-3	Rats and Mice
Amphetamine Sulfate	60-13-9	Rats and Mice
Benzaldehyde	100-52-7	Mice
Benzofuran	271-89-6	Rats and Mice
Gamma-Butyrolactone	96-48-0	Mice
D-Carvone	2244-16-8	Mice
Alpha-Chloroacetophenone (CN)	532-27-4	Rats and Mice
p-Chloroaniline	106-47-8	Rats
Ortho-Chlorobenzalmalononitrile (CS)	2698-41-1	Rats and Mice
C.I. Acid Red 114	6459-94-5	Rats
C.I. Direct Blue 15	2429-74-5	Rats
2,4-Diaminophenol Dihydrochloride	137-09-7	Rats and Mice
Dimethoxane	828-00-2	Rats
3,3'-Dimethoxybenzidine	119-90-4	Rats
N, N-Dimethylaniline	121-69-7	Rats and Mice
3,3'-Dimethylbenzidine	119-93-7	Rats
Diphenhydramine Hydrochloride	147-24-0	Rats and Mice
Epinephrine HCl	55-31-2	Rats and Mice
Ethyl Bromide	74-96-4	Rats and Mice
Furan	110-00-9	Rats
Furfural	98-01-1	Rats
Glycidol	556-52-5	Mice
Hexachloroethane	67-72-1	Rats
Hydrochlorothiazide	58-93-5	Rats and Mice
Hydroquinone	123-31-9	Rats and Mice
8-Methoxypsoralen	298-81-7	Rats
Alpha-Methylbenzyl Alcohol	98-85-1	Rats and Mice
Monochloroacetic Acid	79-11-8	Rats and Mice
Nalidixic Acid	389-08-2	Rats
Nitrofurazone	59-87-0	Rats and Mice
Ochratoxin A	303-47-9	Rats
Pentaerythritol Tetranitrate	78-11-5	Rats and Mice
Phenylbutazone	50-33-9	Rats and Mice
Phenytoin (Diphenylhydantoin)	57-41-0	Rats and Mice
Probenecid	57-66-9	Rats and Mice
Quercetin	117-39-5	Rats
Resorcinol	108-46-3	Rats and Mice
Rhodamine 6G	989-38-8	Mice
Sodium Azide	26628-22-8	Rats
Succinic Anhydride	108-30-5	Rats
Tetranitromethane	509-14-8	Rats and Mice
Titanocene Dichloride	1271-19-8	Rats
Toluene	108-88-3	Rats and Mice
Tris (2-Chloroethyl) Phosphate	115-96-8	Rats and Mice
Vinylcyclohexene Diepoxide	106-87-6	Rats and Mice
Vinyl Toluene	25013-15-4	Rats and Mice

TABLE 19

INTERIM SACRIFICE STUDIES REVIEWED DURING FY 1986

	CAS NO.
C.I. Pigment Red 3, 15 Months (Mice)	2425-85-6
C.I. Pigment Red 23, 15 Months (Rats)	6471-49-4
Talc, 27 Weeks (Rats and Mice)	14807-96-6
Talc, 47 Weeks (Rats)	14807-96-6

CUTANEOUS TOXICOLOGY

The likelihood of the skin being exposed to toxic chemicals is extremely high--it is exposed in the occupational setting, while using chemicals at home, and to a wide range of cosmetic and toiletry formulations and drugs in a variety of vehicles. Within the NTP, the potential of chemicals to produce skin irritation, sensitization, and tumors, and the ability of chemicals to be absorbed through the skin are being studied.

NTP is a member of the DHHS Ad Hoc Interagency Dermatology Working Group. Information from agencies outside of NTP is useful in planning future NTP research activities.

NIEHS

FY 1986 ACCOMPLISHMENTS

Toxicity Evaluation Studies -- NTP develops chemical specific protocols designed to examine the toxicity by the most usual route of exposure to humans. NIEHS is presently evaluating the carcinogenic and toxicologic properties of 19 chemicals following dermal exposure to rats and mice. (CONTACT PERSON: Dr. W. Eastin)

Initiation/Promotion Studies -- Some chemicals are identified as potential tumor promoters based either on results from long-term studies or on a structure-activity relationship with a known promoter. For the mouse skin initiation/promotion studies, a basic study design was prepared to help provide more uniformity among these studies and can be expanded to meet chemical-specific testing requirements. Data from tests to determine a responsive animal model for dermal initiation promotion studies to be used by the NTP have been collected and are currently under evaluation. (CONTACT PERSON: Dr. W. Eastin)

Methods Development -- Several in vitro techniques used to obtain data on rates of dermal absorption, effects of various vehicles on absorption, and dermal metabolism in an in vitro system were reviewed. Data collected from in vitro studies are used by chemical managers as an aid in the design of chemical-specific testing when the most usual route of human exposure is dermal. (CONTACT PERSON: Dr. W. Eastin)

Psoralens -- Toxicity to the skin can also occur following ingestion or inhalation of a chemical and its subsequent localization in the skin. A good example of this is seen after oral administration of psoralens; the psoralen localizes in the skin and ultraviolet light (UVA) exposure to the skin causes a psoralen-DNA interaction and subsequent skin toxicity. A study is now underway to determine tumor response after repeated psoralen and UVA light exposure. (CONTACT PERSON: Dr. J. Dunnick)

Flame Retardants -- The NTP is investigating the toxic and carcinogenic properties of the flame retardant 2,2-bis(bromo-methyl)1,3-propanediol (BMP). Prechronic toxicity studies of BMP are in progress. (CONTACT PERSON: Dr. J. Dunnick)

FY 1986 PROGRAM PLANS

Initiation/Promotion Studies -- Analysis and evaluation of data from studies to compare the responses of several mouse strains to known initiators and promoters and to establish baseline data on these chemicals and skin lesions will be completed. Information from these studies should assist in the selection of a mouse strain and of chemicals to use as positive controls for future initiation/promotion studies. (CONTACT PERSON: Dr. W. Eastin)

Methods Development -- Some *in vitro* systems were reviewed. However, the establishment of the most appropriate methodology for obtaining routine measurements on rodent skin *in vitro* will be continued. There will be participation in a workshop on *in vitro* methods for dermal studies. One purpose of this workshop is to review the kinds of technology available and the kinds of data that can be obtained. This information will be helpful in the selection of an *in vitro* system(s) that will provide data on limits of absorption of applied dose, and on the effects of vehicles on chemical absorption. Data from *in vitro* studies will be provided to chemical managers for consideration in the design of *in vivo* toxicity testing. (CONTACT PERSON: Dr. W. Eastin)

NIOSH

The NIOSH program in cutaneous toxicology has focused on the percutaneous absorption of chemicals, and on the skin as a target organ for injury and disease in the workplace. The program has emphasized the following: (a) development of direct quantitative methods for studying the percutaneous absorption of volatile chemicals; (b) identification of chemicals which may pose a risk following percutaneous absorption; (c) dissemination of information intended to educate the occupational health community about the percutaneous absorption potential of chemicals; (d) definition of the role of chronic mechanical trauma in the development of skin disorders; and (e) evaluation of the dermal toxicity (dermal irritancy or allergic contact dermatitis) of selected agents as part of health hazard investigations.

FY 1986 ACCOMPLISHMENTS

Dermal Absorption Studies -- A report describing the general methods and procedures used by NIOSH to study percutaneous absorption of volatile compounds was published in the Journal of Applied Toxicology. A report was also completed which described studies on the percutaneous absorption of toluene, ethylbenzene and aniline in hairless mice following single applications of the pure chemical. When compared to uptake via inhalation at existing or proposed standards, the dermal absorption of toluene and ethylbenzene would not contribute significantly to a worker's body burden under normal work conditions. On the other hand, dermal absorption of aniline may be significant when compared to uptake via inhalation. These results support the skin notation recommended by the American Conference of Governmental Hygienists (ACGIH) for aniline and its analogs. These studies also showed that an indirect correlation exists between the volatility of the compounds and their percutaneous absorption. (CONTACT PERSON: Dr. T. Lewis)

A guinea pig maximization test for contact sensitization potential was conducted on acrolein. Acrolein was found to be, at worst, a weak sensitizer which may be due to the presence of low molecular weight aldehydes such as formaldehyde. (CONTACT PERSON: Dr. T. Lewis)

Proceedings of the 1983 Workshop on "The Chronic Effects of Mechanical Trauma to the Skin" were published in book form (Alan R. Liss, Inc.) and as a special edition of the American Journal of Industrial Medicine. The Workshop emphasized that repeated mechanical trauma to the skin plays an important, but usually unrecognized role in the development of occupational skin disease. A tentative program for a symposium on "Cutaneous Absorption of Chemicals in the Workplace" has been drafted. The symposium will focus on (1) methods of risk assessment, (2) the effectiveness of existing intervention strategies, and (3) the identification of chemicals and factors in the workplace. (CONTACT PERSON: Dr. T. Lewis)

FY 1987 PROGRAM PLANS

Reports on the indirect relationship between dermal absorption and volatility of compounds, and on guinea pig sensitization to acrolein will be submitted for publication. Studies on the dermal absorption of the insect repellant, N,N-diethyl-m-toluamide, will be completed. The results will be compared to existing data derived by other methods and in other species. The repeated application method for studying percutaneous absorption of volatile chemicals will be tested using benzene as the model compound. A RFC will be submitted for the administration of the symposium on "Cutaneous Absorption of Chemicals in the Workplace" that will take place in Cincinnati in FY 1988. (CONTACT PERSON: Dr. T. Lewis)

IMMUNOTOXICOLOGY

Traditional methods for toxicological assessment have implied that the immune system is a frequent target organ of toxic insult following chronic or acute exposure to environmental chemicals, therapeutic drugs, abused drugs, or radiation. Interaction of the immune system with these xenobiotics may result in undesirable effects of three principal types: 1) those manifested as immunosuppression; 2) those manifested as immune dysregulation (autoimmunity); and 3) those manifested as an immunologic response to the xenobiotic (allergy). The extent of chemical-induced hypersensitivity disease has been known for some time. Stimulated by numerous published reports, the toxicology community has recently become aware that a broad spectrum of chemical xenobiotics can suppress the immune system and increase susceptibility to challenge with infectious agents or tumor cells. Several clinical studies in humans have demonstrated a parallel effect on immune dysfunction. For example, it has been observed that individuals accidentally exposed to polychlorinated biphenyl contaminated rice oil, polybrominated biphenyl contaminated dairy products, or isothiocyanate-derived, imidazolidinethion-adulterated rape seed oil exhibit immune dysfunction. Benzene-induced pancytopenia in factory workers, a symptom of chronic benzene exposure, is also an immunodeficiency disease by virtue of reduced numbers of immunocompetent cells resulting from altered marrow function. These incidents are of concern because of the known association between the therapeutic use of chemical immunosuppressants and increased incidences of infectious disease, neoplastic transformation, and monoclonal gammopathies. Whether exposure to chemical xenobiotics present in the environment affect the immunocompetence of the general population (excluding therapeutic or inadvertent exposure) has not been determined and remains a critical issue.

Correlation of such immunological findings with altered host susceptibility and the extrapolation of these chemically-induced effects to humans is of major concern to the NTP Immunological Toxicology Program. The objectives of the Program are to systematically: 1) evaluate and examine the influence of selected environmental chemicals on the immune system in the whole animal as well as at the cellular level; 2) relate alterations in immunological functions to both general toxicity as well as specific organ toxicity; 3) relate changes in immunological functions with altered host resistance following challenge with tumor cells or infectious agents; and 4) refine and employ a panel of immune and host resistance procedures in order to better define *in vitro* and *in vivo* immunotoxicity.

NIEHS

FY 1986 ACCOMPLISHMENTS

Methods Development and Validation: A document describing the development and validation of a testing battery to assess chemical-induced immunotoxicity has been prepared. This battery represents a comprehensive testing panel composed of two tiers which can reproducibly characterize immune alterations that occur following *in vivo* chemical exposure in mice. In addition to sensitivity and reproducibility, the immunological assays utilized have been correlated to alterations in host resistance to challenge with specific infectious agents or tumor cells. For the most part, the assays demonstrated clear dose-response effects with a no-effect level being obtained for each prototype chemical examined. The correlation observed between functional measurements and challenge models, albeit preliminary, provided insight into the biological significance of each of the various measures of immune function studied. Hopefully, this type of analysis will provide a better understanding of the relevant immune effector mechanism(s) involved in host resistance. Additional qualitative and quantitative information in this area should improve the accuracy with which the effects of chemicals or drugs on the immune system can be predicted.

Neutrophils constitute the main cellular defense system of higher organisms against bacteria. Additionally, they have been implicated as effectors in tumor cell destruction and mediators of certain immune responses. As the importance of neutrophils has become increasingly recognized, it became essential to develop an effective assay panel to measure adverse effects on this cell type. Studies are being conducted to develop a model system in the mouse which will allow the assessment of adverse effects of chemical xenobiotics on neutrophils. A system has been developed that provides a means to obtain a large number of neutrophils from the peritoneal cavity. This system has the advantage that the recovered neutrophils are in their basal state. Activation is induced *in vitro* with phorbol myristate acetate, bacterial agents or synthetic peptides. Our present results suggest that selective parameters of neutrophil activity including leukotriene B4 production, chemotaxis, oxygen radical production, receptor quantitation and antitumor activity represent sensitive constituents of an assay panel which will allow the evaluation of neutrophil activity.

Testing: The immunotoxicology contract laboratory (Medical College of Virginia/Virginia Commonwealth University) has examined a number of compounds of interest to the NTP for their potential to induce either immune alterations (assessed using the testing panel) or hypersensitivity. Immunotoxicity testing has been completed on lithium carbonate and tetraethyl lead. Exposure to tetraethyl lead caused suppression of humoral immunity which correlated with changes in host resistance to infectious agents. Lithium carbonate did not influence immune function following a 14-day exposure in mice. Compounds examined for potential sensitizers included nitrophenylpentadiene (NPPD) and glutaraldehyde. NPPD was found to be a weak skin irritant in the guinea pig but was not a sensitizer when tested in the guinea pig or mouse. Glutaraldehyde was also negative for skin sensitization when examined in the mouse. The in-house research group examined the immunotoxicity of methyl isocyanate in mice following exposure by inhalation. Although there were some slight immunological changes, there were no marked effects by methyl isocyanate on host resistances, indicating that the immune system is not a primary target of methyl isocyanate toxicity.

Basic Studies: Investigations have continued on the alterations in stem cell- and B cell-differentiation caused by 2,3,7,8- tetrachlorodibenzo-p-dioxin (TCDD). During the past year the development of an *in vitro* system previously described (B cell maturation) has provided the following observations: 1) The ability of TCDD to modulate stem cell- and lymphocyte-differentiation is mediated by the Ah-receptor present in these cells; 2)

Several antagonists for this action have been identified, i.e., alpha-napthaflavone and 1-NH_2-trichlorodibenzo-p-dioxin, both of which act at the Ah receptor level and block TCDD binding; 3) The ability of TCDD to inhibit B cell maturation is due to early changes following lymphocyte activation which can be detected by altered protein phosphorylation. These changes alter the ability of B cells to respond to growth factors; and 4) Addition of supraphysiological levels of these growth factors to lymphocytes in the presence of TCDD restores the abnormal response. Studies are presently focusing on early events in activation which precede protein phosphorylation including phospholipid metabolism and protein kinase activity.

The role of altered arachidonic acid metabolism by benzidine and other co-oxidative substrates on humoral immune function remains under investigation. Inhibitors of arachidonic acid metabolism such as NDGA, indomethacin, BW755C, and quinacrine are being used to determine the relationship between altered arachidonic acid metabolism and inhibition of specific stages of lymphocyte activation. These effects are being correlated with those caused by benzidine and other co-oxidative substrates. Arachidonic acid products are being identified in activated B cells in the presence of these inhibitors using an HPLC system. Similar studies are being conducted using progenitor stem cells from the bone marrow. Further studies will involve the addition of various products of arachidonic acid metabolism such as hydroxyeicsatetraeonic acids (HETEs), prostaglandins, and leukotrienes in order to identify those specific metabolites which are necessary for B cell and progenitor cell maturation.

Studies were undertaken to investigate alterations of B cell function following in vitro addition of two antifolates, methotrexate and trimetrexate. There is a paucity of information concerning the effects of methotrexate, a widely used chemotherapeutic agent, on the immune system. Trimetrexate is a "nonclassical antifolate" (i.e., lacking a glutamate residue) that is currently in NCI clinical trials. Studies using an in vitro model of differentiation [B cell maturation to antibody forming cells (AFC)] showed that both drugs markedly inhibit the formation of AFC at concentrations at or below those found in blood of patients undergoing chemotherapy. Studies using acridine orange, for two parameter cytometric analysis (DNA, RNA), have shown that these drugs interrupt normal cell cycle progression of stimulated lymphocytes with a slow accumulation of cells in S/G2+M phase. Reversal of the drug-induced inhibition of AFC formation is observed with the addition of folinic acid. In addition, a complete reversal of AFC inhibition is seen when hypoxanthine is added to cultures while only partial reversal is observed with thymidine addition, indicating that inhibition of pyrimidine biosynthesis by these drugs is secondary to the inhibition of purine biosynthesis in plasma cells. (CONTACT PERSON: Dr. M. Luster)

FY 1987 PROGRAM PLANS

The immunotoxicology contract laboratory will continue to examine selected chemicals for their potential to induce hypersensitivity, altered host resistance, or immunological changes using the standard protocol. Studies will be conducted on gallium arsenide and nitrotoluenes.

Intramural research will continue studies on the elucidation of mechanisms that mediate chemically-induced immunotoxicity. Experiments will focus on alterations in lymphocyte proliferation and differentiation induced by various chemical classes including aromatic amines and polyhalogenated aromatic hydrocarbons. (CONTACT PERSON: Dr. M. Luster)

NEUROBEHAVIORAL TOXICOLOGY

Behavioral and neurologic alterations in response to environmental agents often represent the earliest manifestations of toxicity. One aspect of the NTP Program involves the development, standardization, and validation of tests to assess environmental agents for potential neurotoxicity. The NTP research program is also dedicated to the study of the behavioral and neural effects of environmental agents and to the elucidation of their mechanisms of action. In addition, the program is concerned with the compensatory or adaptive processes activated following exposure to these agents. Information derived from such research may be useful in developing of strategies to treat exposed individuals as well as providing a basis for understanding environmentally-related neurological diseases.

NIEHS

FY 1986 ACCOMPLISHMENTS

Basic Neurobehavioral Studies --- The neuropharmacological basis for tremor and hyperexcitability produced by p,p'-DDT and chlordecone was compared in a series of experiments. Pretreatment with phenytoin, an anticonvulsant that decreases membrane excitability by holding sodium channels in the inactivation state, was used to study the functional significance of brain neurochemical changes produced by p,p'-DDT and chlordecone. Phenytoin selectively enhanced chlordecone-induced tremor and significantly increased chlordecone-induced changes in brainstem methoxyhydroxyphenylglycol (MHPG), the major metabolite of the neurotransmitter norepinephrine. Regional levels of norepinephrine were not affected by p,p'-DDT or chlordecone. Phenytoin blocked tremor as well as increases in brainstem MHPG that are induced by p,p'-DDT. Subsequent experiments found that systemic administration of phenoxybenzamine attenuated the tremor and hyperexcitability produced by chlordecone and p,p'-DDT, suggesting that tremor and hyperexcitability produced by p,p'-DDT and chlordecone are produced by different mechanisms, but are mediated by a common neural pathway. A facilitatory noradrenergic influence, perhaps from pathways descending from the locus ceruleus to the ventral horn, appears to be activated by both agents. Subsequent studies found that systemic administration of alpha-1-noradrenergic receptor antagonists attenuated the tremorigenic effects of p,p'-DDT, while yohimbine, an alpha-2-receptor antagonist, exacerbated the effects of p,p'-DDT. That p,p'-DDT and chlordecone act by different mechanisms is supported by experiments showing that intraventricular administration of calcium into the lateral cerebroventricles exacerbated the effects of chlordecone, but decreased those produced by p,p'-DDT. Furthermore, pretreatment with difluoromethylornithine (DFMO), an irreversible inhibitor of ornithine decarboxylase, attenuated the effects of chlordecone, but had no effect in rats treated with p,p'-DDT. Putrescine, the product formed by ornithine decarboxylase, reversed the effects of DFMO on chlordecone. (CONTACT PERSON: Dr. H. Tilson)

Research was initiated to develop models of cognitive dysfunction using neurotoxicants as tools to mimic specific aspects of neurological diseases known to exist in humans. Cognitive dysfunction is frequently associated with cholinergic hypofunction or damage to the limbic forebrain; cytotoxicants were administered directly into the brain to mimic these processes. Injection of ethylcholine mustard aziridinium ion (AF64-A), a purported cholinergic cytotoxicant, produced behavioral effects indicative of cholinergic dysfunction in rats, including hyperactivity and deficits in spatial learning. However, other studies indicated that this agent may have direct effects on other neurotransmitter or neuromodulator systems. However, direct administration of colchicine into the hippocampus caused preferential damage to the granule cells and mossy fibers of the dentate gyrus. These alterations were associated with deficits in spatial learning and acquisition and retention of an avoidance task and altered sensitivity to challenge with scopolamine, a muscarinic receptor antagonist. Primary studies showed that behavioral and histopathological damage produced by colchicine was attenuated by pretreatment with gangliosides. Future studies will: 1) replicate and extend the finding that gangliosides protect against the effects produced by colchicine, as well as those produced by another cytotoxicant such as 6-hydroxydopamine, 2) determine possible restorative effects of gangliosides, 3) investigate other models of cognitive dysfunction such as the effects of administration of ibotenic acid into the nucleus basalis of Meynert, and 4) evaluate pharmacological agents such as physostigmine and analogues of arecoline as to their potential activity against colchicine-induced degeneration of the hippocampus. (CONTACT PERSON: Dr. H. Tilson)

FY 1987 PROGRAM PLANS

Basic Neurobehavioral Studies --- Pharmacological agents will be administered directly into the spinal cord to determine more precisely the role of descending noradrenergic pathways in the modulation of motor outflow. Based upon these studies, experiments concerning descending serotonergic pathways will be considered.

More extensive experiments will be done on the effects of neuractive agents on retention capabilities of rats. Effects on relatively complex spatial learning tasks will also be studied.

The organochlorine agents produce many physiological effects possibly mediated at the level of the brainstem. For example, chlordecone produces a biphasic decrease followed by an increase in body temperature; other agents such as p,p'-DDT cause hyperthermia only. Preliminary studies have indicated that the chlordecone-induced hypothermia may be related to vasodilation caused by an action on vasomotor systems in the brainstem. Additional studies are planned to investigate this possibility.

Research with the colchicine model of hippocampal dysfunction will continue. The effects of various doses of colchicine on neurobehavioral function, including acquisition and retention of an avoidance task and motor activity, will be studied. In addition, the time-dependent effects of intrahippocampally administered colchicine (1 to 12 weeks postdosing) will be determined, including neurobehavioral (learning and memory, motor activity), histopathological, and neurochemical measures. The effects of colchicine will be studied using various models of cognitive function, including acquisition and performance of a spatial learning task (radial arm maze) and performance of a discriminated Y-maze task.

Behavioral deficits quantified in animal models will be used to determine pharmacological effectiveness of agents proposed for use in humans having cognitive deficits. The first agent will be physostigmine, an acetylcholinesterase inhibitor. Other agents to be considered are a series of conformationally constrained bicyclic compounds similar to the muscarinic cholinergic agonists arecoline and norarecoline. Potential beneficial effects of these agents (i.e., attenuation of behavioral deficits) will be compared to possible side effects (i.e., cholinergic overstimulation).

The potential beneficial effects of gangliosides on colchicine-induced behavioral and histopathological measures will be studied in greater detail. If our previous results with colchicine can be replicated, then the activity of this preparation will be determined using another model of cognitive dysfunction. (CONTACT PERSON: Dr. H. Tilson)

NIOSH

FY 1986 ACCOMPLISHMENTS

Methods Development -- The behavioral test battery recommended by the World Health Organization (WHO) was assembled, and an implementation plan for its international application was developed. The proceedings of a conference held in Cincinnati to discuss implications of the collaborative behavioral teratology study was published. (CONTACT PERSON: Dr. K. Anger)

Spray Paint Solvents -- A total of 180 volunteer subjects were exposed to methyl ethyl ketone (MEK) or acetone at the NIOSH recommended maximum concentrations for workplace exposures, or in combination at half these concentrations; ingested ethanol was used as a positive control. Subjects were tested for changes in behavioral performance using measures of vigilance, choice reaction time, memory and body sway, with blood and breath measures taken concurrently for correlation of concentrations with effects. Also, a review of laboratory research measuring behavioral performance was prepared for publication in the first Handbook on Neurobehavioral Toxicology. (CONTACT PERSON: Dr. R. Dick)

Aliphatic Carbon Solvents -- Adult rats were exposed to low levels of n-hexane, methyl ethyl ketone (1000 ppm), ethyl benzene, xylene (300 ppm) or ethyl benzene plus xylene (150+150 ppm), and tested for behavioral impairments using startle reflex and motor activity measures. (CONTACT PERSON: Dr. J. Russo)

Neurotoxic Chemicals -- A national strategy to prevent neurotoxic disorders was developed, and a review of the National Occupational Hazard Survey data identified roughly 7.7 million full-time workers exposed to neurotoxic chemicals. Papers were published on the neurotoxic effects of mercury and mixed solvents in humans. (CONTACT PERSON: Dr. K. Anger)

FY 1987 PROGRAM PLANS

Methods Development -- The WHO behavioral test battery will be used to assess worker populations, and other methods will be implemented for use in worksite research. Strategies to assess reliability will be implemented to determine the value of the various tests under consideration in this project. (CONTACT PERSON: Dr. K. Anger)

Spray Paint Solvents -- Four-hour exposures of human volunteers to MEK and methyl isobutyl ketone (MIBK), singly and in combination, will be conducted using tests of alertness, speed of reaction, memory, and body sway to identify adverse effects. Blood and breath measures will be taken to determine body burden for correlation with behavioral effects. (CONTACT PERSON: Dr. R. Dick)

Aliphatic Carbon Solvents -- Adult rats will be exposed for four hours to high levels (5000 ppm) of n-hexane, methyl ethyl ketone, methyl n-amyl ketone, and n-pentane to determine if behavioral changes in startle reflex and activity will result and to identify short-term exposure levels that may affect behavior and impair response to crises. (CONTACT PERSON: Dr. J. Russo)

Metals -- A protocol will be completed to study the effects of workplace exposure to toxic metals using neurobehavioral tests. (CONTACT PERSON: Dr. K. Anger)

PULMONARY TOXICOLOGY

Contaminated air is a major source of human exposure to toxins both occupationally and environmentally. Because of the extensive surface area (80 M^2 in humans) of the pulmonary system brought into intimate contact with any inhaled substance, the lung is often the target organ or the place where absorption into the body occurs. Epidemiologists are finding that pulmonary dysfunction is a principal predictor of mortality resulting from pulmonary and non-pulmonary disease. It is reasoned that pulmonary dysfunction leads to increased accumulation of toxicants and thereby acts as an initiator, promoter, or cofactor in the pathogenesis of numerous diseases. Hence, the evaluation of toxicants by inhalation exposure and the toxicologic evaluation of the structure and function of the lung are of critical importance.

NIOSH

One of the objectives of the NIOSH program in pulmonary toxicology is to compare measures of pulmonary function with pathologic indices as predictors of respiratory disease in animal species -- tests of mechanical properties, gaseous distribution, static and dynamic lung volumes, distribution of inspired air, and more recently, ventilatory performance. Pulmonary function testing, in some cases, may be the only indication of toxicity to the lung from inhaled substances. Pulmonary function tests must be reproducible, sensitive, specific, and capable of large-scale utilization if they are to be used effectively in the diagnosis of early and subtle pulmonary lesions in experimental animal models that mimic chemically-induced pulmonary disease in humans.

FY 1986 ACCOMPLISHMENTS

Fibrogenicity of Coal Slags -- A study to evaluate the fibrotic potential of four coal slags is nearing completion. The coal slags were administered by a single intratracheal instillation (40 mg in water) to Sprague-Dawley rats. Groups of rats were killed two days following instillation and at 3, 6, and 12 months. Pulmonary function measurements were taken at these later times. Histopathological evaluation of the tissues is ongoing. (CONTACT PERSON: Dr. L. Stettler)

Pulmonary Hypersensitivity of Industrial Agents -- The results of an initial pilot study on the potential of vanadium pentoxide (V_2O_5) to produce asthma-like reactions following acute inhalation of V_2O_5 dust was published in the American Review of Respiratory Diseases. Investigation into the action of V_2O_5 in the production of asthma continued. Procedures were developed to generate, sample, and analyze the V_2O_5 dust aerosols. Base line bronchial challenge, skin tests, and pulmonary function testing were completed. (CONTACT PERSON: Mr. E. Knecht)

Model for Delayed Asthma -- In a pilot study, cynomologus monkeys were injected subcutaneously with phthalic anhydride-monkey serum albumin (PA-MSA) conjugates or phthalic anhydride (PA) alone. Increased levels of PA-specific IgG and positive skin test conversions were observed, but there were no changes in PA-MSA RAST results or total sera IgE. These data indicate that PA-MSA injections cause skin sensitivity in monkeys. In addition, the significant levels of PA-specific IgG suggest that this parameter may be a useful index of PA exposure in field studies. (CONTACT PERSON: Dr. R. Biagini)

A method for generating and measuring known concentrations of formaldehyde for clinical bronchoprovocation challenge was developed. (CONTACT PERSON: Dr. R. Biagini)

1987 PROGRAM PLANS

Pulmonary Hypersensitivity of Industrial Agents -- The study of the asthmagenic potential of V_2O_5 will be submitted for publication. The potential changes in specific bronchial reactivity, skin sensitivity, and immune profiles will be determined to quantitatively characterize the mechanisms of asthma induction by vanadium. Differences in dosing regimen will be compared to determine induction potential. (CONTACT PERSON: Mr. E. Knecht)

NIEHS

INHALATION TOXICOLOGY

The inhalation Toxicology group designs and conducts studies of compounds administered by inhalation and develops the technology necessary to execute them. Exposures to particulates and gases are conducted by an on-site contractor, Northrop Services, Inc. Studies measure a variety of toxicological endpoints and usually involve the participation of other groups within the NIEHS.

FY 1986 ACCOMPLISHMENTS

Acute and short-term exposures to methyl isocyanate were performed as part of the NTP response to the need for toxicological data on the effect of acute exposure to this compound as a result of the accident at Bhopal, India. An exposure to 1,3-butadiene was also conducted to provide a positive control for a 24-month carcinogenicity assay as part of these studies. The successful and timely completion of this series of technically difficult exposures demonstrates the capabilities of both the automated exposure facility and the on-site contractor.

Short-term exposures to chrysotile asbestos and to silica dust continue to be performed in support of the Laboratory of Pulmonary Pathobiology in the Intramural Research Program. Smaller chambers and animal holding space are being added to the particulate exposure room to provide better support for these studies.

An evaluation of the toxicity of compounds used in the semiconductor industry is being performed in studies conducted in collaboration with several other groups within NTP. The objective of a series of inhalation exposures currently in progress is to define the effects of short-term exposures to arsine. Since workers in the semiconductor industry may be exposed to both arsine gas and gallium arsenide aerosols, the possibility of an interactive effect will also be examined.

Significant improvements are being made in both the control of exposure environments and the management of data resulting from exposures. Gas chromatographs with photo ionization detectors have been incorporated into the monitoring system enabling arsine to be detected at concentrations as low as 5 ppb. The data management system is being upgraded to improve performance, to allow more versatility in intercomputer communications, and to make both environmental and physiological measurements readily available.

Technological capabilities have proven critical to the success of several studies. The ability to control exposure chambers with little human intervention during the actual exposure has allowed studies of extremely toxic compounds such as MIC and arsine to be conducted safely. The ability to accurately monitor the exposure environment has provided both a well-defined exposure environment and a reliable measure of the containment of hazardous compounds.

Research involving many collaborators has required considerable flexibility in accommodating protocol changes and in the analysis of the resulting data.

A preliminary design for a new inhalation facility has been completed. The design provides for flexibility in study design, better animal care facilities, and improved safety and efficiency in daily operations.

FY 1987 PROGRAM PLANS

A two-year exposure to methylene chloride for an NTP carcinogenicity study will be started later this year. Pharmacokinetic parameters quantifying the absorption and metabolism of methylene chloride and the change in these parameters with age will be determined along with other measures related to tumor development.

Work continues on software to support the simulation of physiologically based models on digital computers. Simulations of the disposition of compounds administered by inhalation will aid the design and interpretation of future inhalation studies. A simulation of methylene chloride absorption and metabolism is being constructed. (CONTACT PERSON: Mr. M. Moorman)

REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY

This program area is developing a wide range of techniques for evaluating potential toxic effects of chemical exposure on the reproductive system and developing embryo as well as improving current testing procedures for uncovering such effects. Several new testing procedures have been initiated with the goal of screening larger numbers of chemicals. With these underway, research efforts are beginning to focus more on better defining toxic endpoints and developing information on cellular effects and alterations in underlying processes and how these are related to the ultimate outcome of reproductive or developmental toxicity.

FY 1986 ACCOMPLISHMENTS

The Coordinating Group, made up of representatives from NCTR, NIEHS, and NIOSH, met regularly to review ongoing programs, to assign new test chemicals to appropriate testing programs, and to plan further efforts for addressing program needs. The NTP Board of Scientific Counselors and its Reproductive and Developmental Toxicology Program Review Subcommittee reviewed the entire NTP Reproductive and Developmental Toxicology Program during 1986. Future plans have incorporated recommendations of reviewers.

NCTR

The NCTR effort focuses primarily on a program to develop techniques for evaluating ovarian toxicity. This program uses tissues from female animals in the continuous breeding studies conducted by the NTP.

FY 1986 ACCOMPLISHMENTS

Considerable progress was made on the Interagency Agreement between NTP and NCTR/University of Arkansas in the development and implementation of techniques for evaluation of ovarian toxicity. Ovaries from continuous breeding reproduction studies have been sent to NCTR for evaluation. The technicians at NCTR have been trained for examination of the ovaries and the computer programs have been written to collect data from these examinations. Ovaries from females from the first reproduction studies are currently being examined. (CONTACT PERSONS: Dr. D. Mattison, UAMS/NCTR and Dr. B.A. Schwetz, NIEHS)

FY 1987 PROGRAM PLANS

Studies will continue to evaluate the relationship between morphological features of the mouse ovary and chemical-induced effects on fertility. Ovaries collected from female mice, after effects on fertility have been evaluated in continuous breeding studies, will be used. The fixed ovaries will be processed, sectioned serially, and follicles counted by stage of development. These morphological features will be compared to fertility and reproduction findings in the continuous breeding studies. (CONTACT PERSON: Dr. B.A. Schwetz, NIEHS)

NIEHS

FY 1986 ACCOMPLISHMENTS

Fertility Assessment by Continuous Breeding -- This was the fourth year of studies and all 48 study reports have been completed (Table 20). Chemicals have been studied from the glycol ether, polyglycol, phthalate ester, and methyl xanthine classes of chemicals as well as miscellaneous chemicals. The study protocol has undergone minor modifications as the testing has progressed over the past four years and is currently designed to evaluate two generations exposed to the chemical and concentrates on effects on fertility and offspring assessment. Studies under newly awarded contracts will be initiated late this year. (CONTACT PERSON: Dr. R. Morrissey)

Sperm Morphology and Vaginal Cytology Evaluation -- The sperm morphology and vaginal cytology evaluation has become a standard part of 90-day prechronic toxicity studies, and new data have become available as the prechronic studies are completed. In FY 1986 over twenty chemicals were evaluated using this system. The data are incorporated into the prechronic reports by the contract laboratories. (CONTACT PERSON: Dr. R. Morrissey)

Male Reproductive Toxicology -- Work has focused on Sertoli-enriched cultures from 18-day-old rats. A method to differentiate peritubular cells was identified and validated. These cultures were evaluated as a test system using 2,5-hexanedione (2,5-HD), mono-2-ethylhexyl phthalate (MEHP) and acrylamide as model toxicants. Mechanistic studies are ongoing with 2,5-HD and MEHP, using cytoskeletal immunofluorescence patterns, metabolic secretions, and radiotracer incorporation studies to determine the initial site of action for these compounds. A study is underway to evaluate the ability of plasma androgen binding protein levels to identify and predict male reproductive toxicity. (CONTACT PERSON: Dr. R. Chapin)

Developmental Toxicity and Aromatic Halogenated Hydrocarbons -- Studies continue on the interactions of different halogenated hydrocarbons and their ability to alter normal development. Compounds are administered separately and in combination, and the effects of combined chemical exposures are evaluated in the offspring. (CONTACT PERSONS: Dr. L. Birnbaum and Dr. R. Morrissey)

Methyl Isocyanate Toxicity Studies -- Studies were conducted in-house in Swiss (CD-1) mice to evaluate the potential of inhaled vapors of methyl isocyanate (MIC) to affect reproduction and development. Inhaled MIC at concentrations of 0, 1 or 3 ppm, six hours per day during days 14 through 17 of gestation, caused a significant increase in the number of dead fetuses at birth and caused a significant decrease in neonatal survival during lactation. In contrast, exposure of male and female mice to 1 or 3 ppm given six hours per day for four consecutive days, had no effect on reproduction during mating trials conducted 1, 8 and 17 weeks after the exposure period. Similarly, there was no evidence of a dominant lethal effect in exposed male mice. (CONTACT PERSON: Dr. B.A. Schwetz)

Postnatal Toxicology -- Efforts are in progress to improve our ability to characterize the toxicity of chemicals to neonates relative to adults, and to explore the role of lactation in the induction of neonatal toxicity. Studies were completed which characterized the testicular and hepatic toxicity of diethylhexylphthalate (DEHP) in neonatal and adult rats of different ages. Also begun was a comparison of the rates of intestinal hydrolysis of DEHP at different ages. The recovery of the testis from damage caused by DEHP administration during the neonatal period was assessed. In addition, studies were performed to determine the effects of DEHP on neonatal rats when DEHP was administered to their lactating mothers, and methods were developed to determine the amounts of DEHP and monoethylhexylphthalate (MEHP) secreted into the milk of these rats. (CONTACT PERSONS: Dr. L. Dostal and Dr. B. Schwetz)

Evaluation of Two In Vitro Teratogenesis Screening Systems -- The protocols for the mouse ovarian tumor (MOT) cell attachment and the human embryonic palatal mesenchyme (HEPM) cell assays have been standardized by two independent testing laboratories. Testing has been completed on 44 coded compounds in each laboratory. Reports will be finalized at the completion of these studies. (CONTACT PERSON: Dr. R. Morrissey)

Conventional Teratology Testing -- The testing of chemicals for teratogenicity has continued on contract in FY 1986 (see Table 21). Selection of chemicals for conventional teratology testing in FY 1987 is underway, and is based on results of short-term in vivo reproductive toxicity and fertility assessment by continuous breeding assays, and on literature reviews of nominated chemicals. (CONTACT PERSON: Dr. R. Morrissey)

FY 1987 PROGRAM PLANS

Fertility Assessment by Continuous Breeding -- The system will be used to test a limited number of chemicals per year and various strains and species will be evaluated to further optimize the testing system. Chemicals to be tested include: acrylamide, bromoform, chloroform, 2-ethylhexanol, mono-(2-ethylhexyl) phthalate, nitrofurantoin, and 4-vinylcyclohexene. (CONTACT PERSON: Dr. R. Morrissey)

Sperm Morphology and Vaginal Cytology Evaluation -- This special study will continue to be used as a part of the prechronic studies procedures and 9-month interim sacrifices in the chronic studies. A review of the first 55-60 studies completed under this contract is planned, with re-evaluation of endpoints currently measured. Publication of a historical data base is anticipated. (CONTACT PERSON: Dr. R. Morrissey)

Male Reproductive Toxicology -- Work will continue using cultured Sertoli cells to define the site of action of specific toxicants. These studies will focus on cellular intermediary metabolism, in vitro transformation of xenobiotics, and altered secretory capabilities of toxicant-exposed Sertoli cells. For the study on plasma androgen binding protein levels as predictive of reproductive toxicity, final data will be collected and analyzed. (CONTACT PERSON: Dr. R. Chapin)

Developmental Toxicity and Aromatic Halogenated Hydrocarbons -- Studies are continuing on the effects of combinations of various halogenated hydrocarbons on development. These studies serve as models for studies on chemical interactions and toxicity. (CONTACT PERSONS: Dr. L. Birnbaum and Dr. R. Morrissey)

Postnatal Toxicology -- Studies of the excretion of DEHP into rat milk will be completed, including evaluation of the effects of DEHP on milk quantity and composition in lactating rats. The fertility of male rats after different periods of recovery from neonatal exposure to DEHP will be assessed in mating trials. The excretion of cimetidine and its metabolites into rat milk will be determined as will the antiandrogenic effects of maternal cimetidine exposure on suckling male pups. (CONTACT PERSONS: Dr. L. Dostal and Dr. B. Schwetz)

Evaluation of Two In Vitro Teratogenesis Screening Systems -- Results from both laboratories will be compared, a workshop will be held, and recommendations for future use of these two in vitro assays will be made. (CONTACT PERSON: Dr. R. Morrissey)

Conventional Teratology Testing -- Reports for current studies will be completed and testing will continue at the same capacity, i.e., 10-12 studies on 5-6 chemicals in two species per year. (CONTACT PERSON: Dr. R. Morrissey)

TABLE 20

STUDIES ON THE FERTILITY ASSESSMENT BY CONTINUOUS BREEDING PROTOCOL

Chemical	CAS No.	Laboratory*	NTIS No.+ (If available)
9-Aminoacridine	134-50-9	EHRT	PB 86-163128/AS
2,2-Bis(bromomethyl)-1,3-propanediol	3296-90-0	EHRT	PB 86-168341/AS
Bisphenol A	80-05-7	RTI	PB 84-155308
Bisphenol A	80-05-7	RTI	PB 86-103207
Caffeine	58-08-2	RTI	PB 85-101202
Caffeine	58-08-2	EHRT	PB 85-205052/AS
1,2-Dibromo-3-Chloropropane	96-12-8	RTI	PB 85-118644
Di-n-butylphthalate	84-74-2	RTI	PB 85-144798
Diethylene glycol	111-46-6	RTI	PB 85-137123
Diethylene glycol monoethyl ether	111-90-0	RTI	PB 84-181734
Diethylhexylphthalate	117-81-7	RTI	PB 85-137123
Diethylphthalate	84-66-2	RTI	PB 85-118636
Diethylstilbestrol	56-53-1	RTI	PB 84-136746
Diethylstilbestrol	56-53-1	EHRT	PB 85-164283/AS
Di-n-hexylphthalate	84-75-3	RTI	PB 85-249332/AS
Di-n-octylphthalate	117-84-0	EHRT	PB 85-218147
Di-n-pentylphthalate	131-18-0	EHRT	PB 86-118999
Di-n-propylphthalate	131-16-8	EHRT	PB 85-247856/AS
Ethanol	64-17-5	RTI	PB 86-144979/AS

TABLE 20 (Continued)

2-Ethoxy acetic acid	110-80-5	EHRT	PB 85-197960/AS
Ethylene glycol	107-21-1	EHRT	PB 84-241108
Ethylene glycol	107-21-1	EHRT	PB 86-177383/AS
Ethylene glycol monobutyl ether	101-76-2	EHRT	PB 85-226827/AS
Ethylene glycol monoethyl ether	110-80-5	EHRT	PB 85-118651
Ethylene glycol monoethyl ether acetate	111-15-9	EHRT	PB 86-139565/AS
Ethylene glycol monomethyl ether	109-86-4	EHRT	PB 86-120128/AS
Ethylene glycol monomethyl ether	109-86-4	EHRT	PB 86-163136/AS
Ethylene glycol monophenyl ether	122-99-6	RTI	PB 85-146140/AS
4-Hydroxyacetanilide (Acetaminophen)	103-90-2	RTI	PB 85-204667/AS
Lead acetate	301-04-2	RTI	PB 84-208016
Lead acetate	301-04-2	EHRT	PB 85-203032/AS
Methoxy acetic acid	625-45-6	RTI	PB 86-164274/AS
Methyl salicylate	119-36-8	RTI	PB 84-241140
Methyl salicylate	119-36-8	EHRT	PB 85-164283/AS
Oxalic acid	144-62-7	EHRT	PB 86-167053/AS
Propantheline bromide	50-34-0	EHRT	PB 86-160330/AS
Propylene glycol	57-55-6	EHRT	PB 86-140662/AS
Propylene glycol monomethyl ether	107-98-2	EHRT	PB 86-170578/AS
Sodium saccharin	81-07-2	EHRT	PB 85-188258/AS
Sulfamethazine	57-68-1	RTI	PB 84-192160
Theobromine	83-67-0	EHRT	PB 85-120368

TABLE 20 (Continued)

Theophylline	58-55-9	EHRT	PB 85-204659/AS
Trichloroethylene (rat)	79-01-6	RTI	PB 86-190782/AS
Trichloroethylene (mouse)	79-01-6	RTI	PB 86-173150/AS
Tricresyl phosphate	1330-78-5	RTI	PB 86-167277/AS
Triethylene glycol	112-27-6	RTI	PB 85-137073
Triethylene glycol diacetate	111-21-7	RTI	PB 86-161999/AS
Triethylene glycol dimethyl ether	112-49-2	RTI	PB 85-150456/AS

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* EHRT = Environmental Health Research and Testing, Inc.
RTI = Research Triangle Institute
+ NTIS = National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161. Telephone: (703)487-4650.

TABLE 21

DEVELOPMENTAL TOXICITY STUDIES COMPLETED OR IN PROGRESS IN FY 1986

Chemical	CAS No.	Species	Route	Dose Levels*
Studies Completed or in Final Report Stage				
Codeine	76-57-3	Mouse	gavage	0,37.5,75,150,300,450
		Hamster	gavage	0,10,50,150(bid)
Diethylene glycol dimethyl ether	111-96-6	Mouse	gavage	0,62.5,125,250,500
		Rabbit	gavage	0,25,50,100,175
Ethylene glycol	107-21-1	Rat (postnatal)	gavage	0,250,1250,2250
α-Methyldopa	555-30-6	Mouse	gavage	0,100,250,500,750
		Rat	gavage	0,50,100,250,500
Nitrofurazone	59-87-0	Mouse	feed	0,0.0038,0.0075,0.025, 0.050%
		Rabbit	gavage	0,5,10,15,20
Scopolamine	51-34-3	Rat	gavage	0,10,100,450,900
		Mouse	gavage	0,10,100,450,900
Triethylene glycol dimethyl ether	112-49-2	Mouse	gavage	0,250,750,1000
		Rabbit	gavage	0,75,125,175,250
Studies in Progress				
Diethylene glycol diethyl ether	112-36-7	Mouse	gavage	0,1500,3000,4500
		Rabbit	not yet selected	
Ethylene glycol diethyl ether	629-14-1	Mouse	gavage	0,50,150,500,1000
		Rabbit	gavage	0,25,50,100
1,1,1-Trichloroethane	71-55-6	Rat	drinking water	0,3,10,30 ppm (teratology)
		Rat	drinking water	0,3,10,30 ppm (postnatal)

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* Doses are mg/kg/day unless otherwise indicated.

NIOSH

FY 1986 ACCOMPLISHMENTS

Behavioral Teratology of Alcohol Solvents -- Proceedings from the NCTR Collaborative Behavioral Teratology Study were published in a special issue of Neurobehavioral Toxicology and Teratology. Male reproductive and behavioral teratology studies were done following exposure of pregnant rats to 1-butanol at 9,000 mg/m^3. Offspring from these in utero exposures were evaluated for changes in neuromuscular coordination, activity and learning. Brains were analyzed for protein and steady-state concentrations of neurochemicals. Standard teratology studies were also performed with 1-ethyl 2-hexanol and 1-octanol. (CONTACT PERSON: Mr. S. Brightwell)

Functional Teratology -- Papers on the effects of prenatal ethylene glycol monomethyl ether (EGMME) treatment on cardiac function in neonatal rats were published in Teratology and in Drug and Chemical Toxicology. Additional work with EGMME revealed that prenatal treatment with EGMME inhibited rat embryo ornithine decarboxylase (ODC) activity in a dose-dependent manner. The inhibition of ODC activity was associated with the developmental toxicity of EGMME. These data were presented at the annual Teratology Society meeting. (CONTACT PERSON: Dr. M. Toraason)

Short-Term In Vivo Reproductive Toxicity Assay -- A contractor completed testing of 12 chemicals (Table 22) in this assay in which pregnant female mice are dosed with the chemical and pregnancy success determined. An additional 12 chemicals were originally scheduled but could not be tested due to budget limitations. A workshop was held in May 1986 in Cincinnati at which investigators from government, industry, and commercial testing laboratories discussed this short-term in vivo assay system and its status for screening chemicals for potential adverse effects on pregnancy outcome. The consensus was that this is a useful test system which can accurately detect reproductive toxicants. Papers presented at that workshop have been submitted for publication in Teratogenesis Carcinogenesis Mutagenesis. Workshop recommendations are being evaluated and plans made for possible modifications to the test protocol and application of the revised assay in future NTP programs. (CONTACT PERSON: Dr. S. Schrader)

Inhalation Reproductive Toxicity Studies -- Under an interagency agreement between the NTP and the Department of Energy Pacific Northwest Laboratories (DEPNL), 1,3-butadiene and n-hexane were evaluated for induction of dominant lethal mutations in male mice, for effects on sperm head morphology in mice, and for teratogenicity in rats and mice (1,3-butadiene only) following exposures at 200, 1000, and 5000 ppm. The duration of exposure was 6 hours/day for 1,3-butadiene and 20 hours/day for n-hexane. Final reports on all those tests will be available early in FY 1986. Preliminary studies also were completed in preparation for a FY 1987 behavioral teratology study in rats similarly exposed to n-hexane. A teratology study of n-hexane in mice will also be completed in FY 1987. Preliminary evaluation of research needs for tetrahydrofuran is underway and testing will follow n-hexane. Acetone, chloroprene, and isoprene are the next three chemicals selected for testing. (CONTACT PERSONS: Dr. B. Schwetz, NIEHS; Dr. S. Schrader, NIOSH)

Metabolism and Excretion of Diethylene Glycol Dimethyl Ether -- The metabolism of diethylene glycol dimethyl ether (DGDME), an aprotic glycol ether, was studied to identify the chemical species responsible for observed effects on rat fertility. Metabolic formation by rats administered 684 or 6.94 mg/kg was qualitatively the same. The principal metabolite, was identified as methoxyethoxyacetic acid (MEAA). However, when tested in rats, MEAA produced no gross or microscopic changes at a dose level equivalent to that shown to cause such changes using DGDME. A secondary metabolite was identified as methoxyacetic acid, a known reproductive toxin. A paper was presented at the 1986 Society of Toxicology meeting describing the results of this study. (CONTACT PERSON: Mr. D. Richards)

Development of a Short-Term Teratology Screening Method in Drosophila -- The contract, awarded in late FY 1985 to assess the validity of the method, is in progress. The contractor has completed all range-finding studies and approximately 30 of a scheduled 90 screening tests have been completed. A maximum of 47 chemicals, with up to five screening tests per chemical are being evaluated. These chemicals are taken from a list recommended by the *ad hoc* committee for *in vitro* teratogenesis test validation (Smith et al., *Teratogenesis, Carcinogenesis, and Mutagenesis* 3:461-480, 1983). (CONTACT PERSON: Mr. D. Lynch)

Semen Analysis in Animals, Longitudinal and Field Studies -- Data analyses for the ethylene dibromide study conducted in Hawaii and the glycol ether study conducted in Oregon were completed and submitted for publication. The data from the collaborative study between NIOSH and NIEHS evaluating male reproductive effects of ethylene dibromide were presented at the American Society of Andrology annual meeting. The longitudinal study of human semen characteristics was initiated. (CONTACT PERSON: Dr. S. Schrader)

FY 1987 PROGRAM PLANS

Behavioral Teratology of Alcohol Solvents -- Reproductive toxicity, standard teratology and behavioral teratology studies will be performed in rats treated with 1-nonanol and 1-decanol. A behavioral teratology study will test the neuromuscular integrity, activity, sensory function, and learning/avoidance of offspring exposed prenatally to non-teratogenic doses of t-butanol. (CONTACT PERSON: Mr. S. Brightwell)

Short-Term In Vivo Reproductive Toxicity Assay -- Papers presented at the May 1986 Workshop will be published and the testing protocol will be reviewed in light of the information developed at the Workshop. Based on that review, proposals will be made to the NTP Board of Scientific Counselors for appropriate future applications of this assay in the NTP Reproductive and Developmental Toxicology Program. (CONTACT PERSON: Dr. S. Schrader)

Inhalation Reproductive Toxicity Studies -- Final reports of tests conducted in FY 1986 will be completed. Teratology tests in mice and behavioral teratology tests in rats will be conducted for n-hexane. Tests will be chosen for those chemicals already selected for testing: tetrahydrofuran, acetone, chloroprene, and isoprene. Three additional chemicals will be selected for future testing. (CONTACT PERSONS: Dr. B. Schwetz, NIEHS; Dr. S. Schrader, NIOSH)

Metabolism and Excretion of Diethylene Glycol Dimethyl Ether -- Cytochrome P-450-dependent metabolism of diethylene glycol dimethyl ether will be investigated by pretreating rats with phenobarbital or SKF 525A to evaluate the effect of chemical interactions on the reproductive toxicity produced by diethylene glycol dimethyl ether exposure. (CONTACT PERSON: Mr. D. Richards)

Functional Teratology -- Papers on the effects of EGMME and maternal calcium metabolism and embryo ODC activity will be published. The hypothesis that treatment of pregnant rats with EGMME interferes with pregnancy outcome by inhibition of parturition will be tested in a series of cross-fostering studies. (CONTACT PERSON: Dr. M. Toraason)

Development of a Short-Term Teratology Screening Method in Drosophila -- The contractor will continue to test known teratogenic and nonteratogenic chemicals from the list of compounds suggested for in vitro teratology test validation. Approximately 75 of 90 scheduled screening tests will be performed. In-house, dosing requirements will continue to be supplied to the contractor. Additionally, data will be statistically analyzed as they are generated. (CONTRACT PERSON: Mr. D. Lynch)

Semen Analysis in Animals, Longitudinal and Field Studies -- The longitudinal study of human semen characteristics will be completed. A field study evaluating the effects of radio frequency radiation is scheduled. The planning of a symposium on occupational exposures that affect male reproductive potentials will be initiated. (CONTACT PERSON: Dr. S. Schrader)

TABLE 22

CHEMICALS TESTED IN FY 1986 IN THE SHORT-TERM *IN VIVO* REPRODUCTIVE TOXICITY ASSAY

CHEMICAL NAME	CAS NUMBER
Acetone	67-64-1
Benzethonium Chloride	121-54-0
Benzyl Alcohol	100-51-6
Diethanolamine	111-42-2
3-Ethoxy-1-Propanol	111-35-3
Monoethanolamine	141-43-5
Probenecid	57-66-9
trans-Retinoic Acid	302-79-4
13-cis Retinoic Acid	4759-48-2
4,4'-Thiobis (6-t-Butyl-m-Cresol)	96-69-5
Tri-O-Cresyl Phosphate	78-30-8
Triethanolamine	102-71-6

COORDINATIVE MANAGEMENT ACTIVITIES

CHEMICAL NOMINATION AND SELECTION ACTIVITIES

The NTP chemical nomination and selection process was described previously in the chapter titled Chemical Nomination and Selection Process. Accomplishments in FY 1986 and program plans for FY 1987 are described as follows:

FY 1986 ACCOMPLISHMENTS

NTP Chemical Nomination -- During FY 1986 42 chemicals were nominated to the NTP for extensive toxicological testing. Nominating sources had been asked to provide as much background information as possible in a supporting summary document (Table 23); however, all nominations were considered regardless of the extent of the information submitted. Table 24 lists the nominated chemicals, their CAS numbers, the source of the nominations and the recommended tests.

During FY 1986, the NTP support contractor for the chemical nomination and selection process prepared 29 draft Executive Summaries. The contractor completed the entry of relevant data on uses, production, worker exposure, and NTP nomination and selection history on 573 nominated and selected chemicals into the CHEMTRACK on-line data base in FY 1986. CHEMTRACK records of 187 additional chemicals were in the process of being updated at the end of FY 1986.

Evaluation of Nominated Chemicals -- During FY 1986 the Chemical Evaluation Committee (CEC) reviewed 32 chemicals that were previously nominated to the Program and made recommendations based upon whether the chemical satisfies one or more of the eight NTP chemical selection principles (Table 25).

The CEC evaluated seven of these chemicals on October 23, 1985, eleven on January 8, 1986, six on April 29, 1986 and eight on September 16, 1986. Tables 26, 27, 28 and 29 list the chemicals, their CAS numbers, the testing recommendations with priority and CEC remarks.

Genotoxicity -- During FY 1986, three chemicals were nominated for genotoxicity testing. methylene blue, cetyl alcohol, and sodium lauroyl isethionate. On January 8, 1986, the CEC selected methylene blue for testing in the mouse lymphoma assay.

Public Comment -- To solicit public input into the chemical nomination and selection process, Federal Register notices were published in FY 1986 on the chemicals evaluated for extensive toxicological testing at the July 30, 1985, October 23, 1985, January 8, 1986 and April 29, 1986 CEC meetings. The notices which appeared on October 8, 1985, January 24, 1986, March 19, 1986 and June 10, 1986, respectively, requested the submission of relevant data and comments on the testing recommendations.

As a result of these notices information on production and/or toxicology data were submitted by industry on the following compounds: n-butane, n-butyl acrylate, t-butylhydroquinone, 2-chloronitrobenzene, 4-chloronitrobenzene, isopentane, methylcyclopentadienyl manganese tricarbonyl, and styrene. The information was summarized and utilized in the further evaluation of the chemicals.

Peer Review -- On October 30, 1985, the Board of Scientific Counselors reviewed seven chemicals. Two of these chemicals were evaluated by the CEC on February 5, 1985 and five on July 30, 1985. On March 25, 1986, the Board reviewed thirteen chemicals. Five of these chemicals were evaluated by the CEC on October 23, 1985 and eight on January 8, 1986. Two of the seven chemicals, t-butylhydroquinone and styrene, reviewed by the CEC at the October 23, 1985 meeting were agency priority chemicals for carcinogenicity testing, and were submitted directly to the NTP Executive Committee for decision making in accordance with NTP policy for facilitating the processing of such chemicals. Three of the eleven chemicals, reviewed by the CEC on January 8, 1986, bromochloroacetonitrile, dibromoacetonitrile, and dichloroacetonitrile, were not reviewed by the Board because the nominator of these chemicals requested that further evaluation be deferred. The testing recommendations including priority for testing and additional remarks and/or caveats are summarized in Tables 30 and 31.

Chemical Selection -- The Executive Committee selected 8 chemicals as Fiscal Year 1986 priority chemicals for indepth toxicologic evaluation. Two of these chemicals, t-butylhydroquinone and styrene, were participating agency priority chemicals for carcinogenicity testing. The names and CAS numbers of these chemicals are listed in Table 32.

FY 1987 PROGRAM PLANS

Evaluation of Nominated Chemicals -- The Chemical Evaluation Committee (CEC) expects to review 25 to 35 compounds previously nominated for toxicology testing and to select approximately 50 compounds for mutagenicity testing in the *Salmonella* assay.

Public Comment -- *Federal Register* notices will be published to solicit input on the chemicals evaluated by the CEC during FY 1987.

Peer Review -- In FY 1987, the Board of Scientific Counselors will review 25 to 35 chemicals.

Chemical Selection -- It is anticipated that the Executive Committee will select 10 to 15 compounds as the FY 1987 priority chemicals for indepth toxicologic evaluation.

TABLE 23
NTP CHEMICAL NOMINATION ELEMENTS

I. Chemical Identification

- a. Chemical Abstracts Service (CAS) preferred name
- b. Common or generic name and synonyms
- c. CAS Registry Number
- d. Chemical class and related compounds
- e. Physical and chemical properties

  - i. Physical description
  - ii. Structural and molecular formula and molecular weight
  - iii. Melting and boiling points
  - iv. Solubility
  - v. Stability and reactivity
  - vi. Other relevant information

- f. Commercial product(s) composition
- g. References

II. Production, Use, Occurrences, and Analysis

- a. Production

  - i. Source and synthesis, year and pathway of first production
  - ii. Current production and pathway
- b. Uses
- c. Occurrence in the Environment

  - i. Naturally occurring
  - ii. Air, water, and soil
  - iii. Occupational

- d. Analysis
- e. References

III. Toxicology

- a. Human data, case reports, and epidemiological studies
- b. Experimental animal information
- c. In vitro and other short-term tests
- d. Other relevant information
- e. References

IV. Disposition and Structure-Activity Relationships

- a. Absorption, distribution, metabolism and excretion
- b. Structure-activity correlations and considerations
- c. References

TABLE 23 (Continued)

V. Ongoing, Toxicological and Environmental Studies in the Government, Industry, and Academia

VI. Rationale for Recommendation and Suggested Studies

TABLE 24

CHEMICALS NOMINATED IN FY 1986 FOR EXTENSIVE TOXICOLOGICAL TESTING

	Chemical (CAS Number)	Nomination Source	Recommended Testing
1.	Acrolein (107-02-8)	NCI	-Carcinogenicity
2.	Acrylic acid (79-10-7)	NCI	-Carcinogenicity
3.	Aldicarb oxime (1646-75-9)	NCI	-Immunotoxicity
4.	Anthraquinone (84-61-1)	NIEHS	-Toxicology and carcinogenicity studies
5.	Azathioprine (446-86-6)	NIEHS	-Long-term toxicology and carcinogenicity studies
6	Butanal oxime (110-69-0)	NCI	-Carcinogenicity
7.	1,4-Butanediol (110-63-4)	NCI	-Carcinogenicity -Chemical disposition and metabolism
8.	Camphor (76-22-2)	NCI	-Carcinogenicity
9.	Chlordiazepoxide* (58-25-3)	FDA	-Carcinogenicity in mice
10.	1-Chloro-2-bromo-ethane (107-04-0)	NCI	-Carcinogenicity
11.	C.I. Basic Red 29** (42373-04-6)	NCI	-Cell transformation -90-day toxicity
12.	Clorazepate* (23887-31-2)	FDA	-Carcinogenicity

TABLE 24 (Continued)

	Chemical (CAS Number)	Nomination Source	Recommended Testing
13.	Conjugated Estrogens Sodium oestrone sulfate (438-67-5) Sodium equilin sulfate (16680-47-0) Piperazine oestrone sulfate (7280-37-7)	NIEHS	-Long-term toxicology and carcinogenicity studies
14.	Cyclohexanone oxime (100-64-1)	NCI	-Carcinogenicity
15.	Diazepam* (439-14-5)	FDA	-Carcinogenicity in mice
16.	Diethylene glycol (111-46-6)	NCI	-Carcinogenicity -Chemical disposition and metabolism
17.	Diphenylamine (122-39-4)	NCI	-Carcinogenicity
18.	Dipropylene glycol (25265-71-8)	NCI	-Subchronic study including testing for hematological effects -Metabolism -Mutagenicity -Teratogenicity
19.	Echimidine (520-68-3)	Dr. C.C.J. Culvenor	-Carcinogenicity
20.	2-Ethylhexyl acrylate (103-11-7)	NCI	-Carcinogenicity
21.	Fenthion (55-38-9)	NIOSH	-Neurotoxicity
22.	Flurazepam (17617-23-1)	FDA	-Carcinogenicity

TABLE 24 (Continued

	Chemical (CAS Number)	Nomination Source	Recommended Testing
23.	Heptachlor (76-44-8)	Dr. D.R. Mattison	-Multigeneration reproductive study -Fertility assessment by continuous breeding
24.	Heptachlor epoxide (1024-57-3)	Dr. D.R. Mattison	-Multigeneration reproductive study -Fertility assessment by continuous breeding
25.	Isobutene (115-11-7)	NCI	-Carcinogenicity
26.	Lead oxide (Lead monoxide) (1317-36-8)	NIOSH	-Comparative toxicological study of lead oxide and lead sulfide (galena) by inhalation route
27.	Lead sulfide (galena) (1314-87-0)	NIOSH	-Comparative toxicological study of lead oxide and lead sulfide (galena) by inhalation route
28.	Methacrylonitrile (126-98-7)	NCI	-Carcinogenicity
29.	Methyl acrylate (96-33-3)	NCI	-Carcinogenicity
30.	Methylene bisphenyl isocyanate (101-68-8)	United Brotherhood of Carpenters and Joiners	-Bioassay toxicity testing
31.	Methyl isocyanate (624-83-9)	NIEHS	-Prechronic study -Carcinogenicity
32.	Methyl tert-butyl ether (1634-04-4)	NCI	-Carcinogenicity
33.	Oxazepam* (604-75-1)	FDA	-Carcinogenicity in mice

TABLE 24 (Continued)

	Chemical (CAS Number)	Nomination Source	Recommended Testing
34.	Oxymetholone (434-07-1)	NIEHS	-Long-term toxicology and carcinogenicity studies
		NCI	-Immunotoxicity -90-day toxicity
35.	o-Phenanthroline** (66-71-7)	NCI	-Carcinogenicity
36.	Phenylpropanolamine hydrochloride (154-41-6 and 7587-43-1)	NCI	-Mutagenicity -90-day toxicity
37.	Primaclone** (125-33-7)	NCI	-Carcinogenicity
38.	Sulfuryl fluoride (2699-79-8)	NIOSH	-Toxicological evaluation including neurotoxicity study
39.	2-Thiazolamine (96-50-4)	NCI	-Cell transformation -90-day toxicity
40.	Thiazole** (288-47-1)	NCI	-Cell transformation -90-day toxicity
41.	Treosulfan (299-75-2)	NIEHS	-Long-term toxicology and carcinogenicity studies
42.	Trichloromelamine** (7673-09-8 and 12379-38-3)	NCI	-Carcinogenicity

*Previously nominated by NIEHS
**Previously nominated by NCI

TABLE 25

NTP CHEMICAL SELECTION PRINCIPLES

The NTP Executive Committee operates under the principle that industry will test chemicals for health and environmental effects as intended and mandated by the Congress under legislative authorities. Therefore, the NTP, acting under its chemical selection principles, will test:

1. Chemicals found in the environment that are not closely associated with commercial activities;

2. Desirable substitutes for existing chemicals, particularly therapeutic agents, that might not be developed or tested without Federal involvement;

3. Chemicals that should be tested to improve scientific understanding of structure-activity relationships and thereby assist in defining groups of chemicals that should be tested by industry;

4. Certain chemicals tested by industry, or by others, the additional testing of which by the Federal Government is justified to verify the results;

5. Previously tested chemicals for which other testing is desirable to cross-compare testing methods;

6. "Old chemicals" with the potential of significant human exposure which are of social importance but which generate too little revenue to support an adequate testing program (some of these may be "grandfathered" under FDA laws);

7. Two or more chemicals together, when combined human exposure occurs (such testing probably cannot be required of industry if the products of different companies are involved); and

8. In special situations, as determined by the Executive Committee, marketed chemicals which have potential for large-scale and/or intense human exposure, even if it may be possible to require industry to perform the testing.

The selection of a chemical by the Executive Committee does not automatically commit the NTP to testing the chemical. The NTP is committed to ascertain the specific toxicologic and regulatory concerns; evaluate the adequacy of existing data or current efforts in government, academic, or private laboratories; and then propose and conduct specific tests that are needed. Occasionally new information is obtained that answers the questions posed in the nomination and selection process. Sometimes testing is not done because chemicals are withdrawn by the nominator, because others are or will be testing the chemical, or because the chemical is not available, or no longer produced.

TABLE 26

TESTING RECOMMENDATIONS FOR CHEMICALS REVIEWED
BY THE NTP CHEMICAL EVALUATION COMMITTEE
ON OCTOBER 23, 1985

Chemical (CAS Number)	Testing Recommendation (Priority)	Chemical Selection Principles	Rationale/Remarks
1. n-Butyl acrylate (141-32-2)	-Subchronic study -Chemical disposition -Carcinogenicity -Mutagenicity, including *Drosophila* and *in vitro* cytogenetics -Reproductive studies (Moderate)	3,8	-High production -Structural interest in acrylates
2. t-Butylhydroquinone* (1948-33-0)	Carcinogenicity (--)	3,4	-Potential for increasing usage as food additive -Previous chronic study in rats inadequate by present day standards
3. 12-O-Hexadecanoyl-16-hydroxyphorbol-13-acetate (HHPA) (53202-98-5)	No testing	--	-Lack of data indicating potential for exposure
4. Methyl ethyl ketoxime (96-29-7)	-In-depth toxicological evaluation to include behavioral studies by inhalation route -*In vitro* cytogenetics (Low)	3,8	-Structural interest -Gap in knowledge concerning toxicity of oximes -Concern about potential occupational exposure
5. Alpha-Methylstyrene (98-83-9)	-In-depth toxicological evaluation -Short-term *in vivo* reproductive toxicity assay -*In vitro* cytogenetics (Low)	3,8	-High production -Potential for toxicity based on *in vitro* data

TABLE 26 (Continued)

Chemical (CAS Number)	Testing Recommendation (Priority)	Chemical Selection Principles	Rationale/Remarks
6. Styrene** (100-42-5)	-Inhalation carcinogenicity (High)	3,4,5,8	-Need for adequate inhalation study -High occupational exposure -Styrene-7,8-oxide, a metabolite of styrene, is a mutagen and a carcinogen
7. Tung oil (8001-20-5)	No testing	--	-Nomination based on concern that 12-O-hexadecanoyl-16-hydroxyphorbol-13-acetate (HHPA) is a tumor promoter, and a constituent of tung oil. However, no evidence that HHPA is a constituent of commercially available tung oil. Main constituents of tung oil are five long chain fatty acids which are judged to have low potential for toxicity.

*FDA FY 1985 priority chemical for carcinogenicity testing by NTP
**NIOSH FY 1986 priority chemical for carcinogenicity testing by NTP

TABLE 27

TESTING RECOMMENDATIONS FOR CHEMICALS REVIEWED BY THE NTP CHEMICAL EVALUATION COMMITTEE ON JANUARY 8, 1986

Chemical (CAS Number)	Testing Recommendation (Priority)	Chemical Selection Principles	Rationale/Remarks
I. Alkanes			
1. n-Butane (106-97-8)	-Prechronic studies including subchronic study -*Drosophila* sex-linked recessive lethal assay (Low)	3,8	-Potential for high exposure
2. Isopentane (78-78-4)	-Prechronic studies, including subchronic study, and study of neuropathologic effects -*Drosophila* sex-linked recessive lethal assay (High)	3,8	-Potential for high exposure -Suspicion of neurotoxicity on the basis of structural considerations.
II. Chloronitrobenzenes			
1. 2-Chloronitrobenzene (88-73-3)	-Prechronic studies - subchronic studies to include testing for hematopoietic and cardiac effects, sperm morphology vaginal cytology evaluation. -Other reproductive studies judged appropriate by NTP staff (High)	3,8	-Potential for exposure -Known toxicity -Structure activity relationships between isomers -Report of reproductive toxicity in male rats in study of 4-chloronitrobenzene conducted by industry -Review results of subchronic studies regarding advisability of carcinogenic studies for one or both isomers.
2. 4-Chloronitrobenzene (100-00-5)		3,8	

TABLE 27 (Continued)

Chemical (CAS Number)	Testing Recommendation (Priority)	Chemical Selection Principles	Rationale/Remarks
III. Furans			
1. Furan (110-00-9)	No further testing	--	-Sufficient data are available from current NTP carcinogenicity testing to indicate hazard potential of furan -Oral exposure to humans is significant route
2. Furfuryl alcohol (98-00-0)	-Carcinogenicity by inhalation route (Moderate)	3,8	-High exposure -Testing subject to feasibility studies on generation and stability of chemical in atmosphere
IV. Haloacetonitriles			
1. Bromochloroacetonitrile (83463-62-1)	No testing	--	-Not commercially significant -Low occurrence in drinking water -Other halogenated compounds of known toxicity occur in drinking water at higher concentrations -Compounds have transient nature and are not expected to persist in water -Compounds can be removed from water by increasing pH.
2. Dibromoacetonitrile (3252-43-5)	No testing	--	
3. Dichloroacetonitrile (3018-12-0)	No testing	--	

TABLE 27 (Continued)

Chemical (CAS Number)	Testing Recommendation (Priority)	Chemical Selection Principles	Rationale/Remarks
V. Miscellaneous			
1. Catechol (120-80-9)	No testing	--	-Nominated to complete class study of hydroxybenzenes; however, current NTP testing of other hydroxybenzenes is expected to provide sufficient data to characterize toxicity of hydroxybenzenes class. -Metabolism study of benzene will provide information on catechol.
2. Pentamidine isethionate (140-64-7)	No testing	--	-Drug was nominated in order to obtain test data for new drug application (NDA). Drug was recently assigned "orphan drug status" by the FDA allowing it to be manufactured and distributed by one company in the U.S. without prior testing. Basis for nomination no longer exists.

TABLE 28

TESTING RECOMMENDATIONS FOR CHEMICALS REVIEWED BY THE NTP CHEMICAL EVALUATION COMMITTEE ON APRIL 29, 1986

Chemical (CAS Number)	Testing Recommendation (Priority)	Chemical Selection Principles	Rationale/Remarks
1. Cobalt naphthenate (61789-51-3)	No testing	--	-Lack of exposure -EPA will provide data on other naphthenates tested as a result of a test rule promulgated under the Toxic Substances Control Act. -NTP is conducting pre-chronic study on another cobalt compound, cobaltous sulfate.
2. Di(2-ethylhexyl-sebacate (DEHS) (122-62-3)	No testing	--	-Low potential for exposure -NTP has tested a number of compounds containing the 2-ethylhexyl moiety, which is the basis for suspicion of toxicity of DEHS. -Several other compounds (2-ethylhexanol and mono(2-ethylhexyl)-phthalate) are also scheduled for NTP in-depth toxicological evaluation.
3. Methylcyclopentadienylmanganese tricarbonyl (MMT) (12108-13-3)	No testing	--	-Low potential for consumer exposure. Not used in U.S. as a gasoline additive.
4. 2-Methylquinoline (91-63-4)	No testing	--	-Low production -Low potential for exposure
5. 4-Methylquinoline (491-35-0)	No testing	--	

TABLE 28 (Continued)

Chemical (CAS Number)	Testing Recommendation (Priority)	Chemical Selection Principles	Rationale/Remarks
6. 1,3,5-Trichloro-1,3,5-triazine-2,4,6-(1H,3H,5H)-trione (TTT) (87-90-1)	Defer	--	-Because of its high reactivity, TTT would be difficult to test. The chemical is readily hydrolyzed to cyanuric acid and hypochlorous acid. -Deferred in order to obtain and evaluate results of carcinogenicity study of sodium cyanurate conducted by industry.

TABLE 29

TESTING RECOMMENDATIONS FOR CHEMICALS REVIEWED BY THE NTP CHEMICAL EVALUATION COMMITTEE ON SEPTEMBER 16, 1986

Chemical (CAS Number)	Testing Recommendation (Priority)	Chemical Selection Principles	Rationale/Remarks
A. Benzodiazepine drugs			
1. Chlordiazepoxide (58-25-3)	No testing	--	-Declining use -Rat carcinogenicity study already performed -Three other related benzodiazepines recommended for testing -Of five FDA benzodiazepine nominations, chlordiazepoxide was given lowest priority for testing by the FDA.
2. Clorazepate (23887-31-2)	No testing	--	-Available data indicate minimal toxicity. -Three other related benzodiazepines recommended for testing -Of five FDA benzodiazepine nominations, chlorazepate was given next to lowest priority for testing by the FDA.
3. Diazepam (439-14-5)	-Carcinogenicity in mice -Prechronic studies should include sperm morphology testing. (High)	3,4	-Extensive use and human exposure -Lack of carcinogenicity data in mice -"Old" chemical approved for use prior to FDA requirement for carcinogenicity testing and no longer under patent; hence FDA cannot require industry to test.

-Generate data on structure-activity relationships for benzodiazepine drugs

TABLE 29 (Continued)

Chemical (CAS Number)	Testing Recommendation (Priority)	Chemical Selection Principles	Rationale/Remarks
4. Flurazepam (17617-23-1)	-Carcinogenicity in mice and rats -Prechronic studies should include sperm morphology testing. -Fertility assessment by continuous breeding studies -Teratology studies (High)	3,4	-Extensive use and human exposure -Only nominated benzodiazepine which is used as hypnotic -Lack of carcinogenicity data in rodents -Due to fluorine substituent, flurazepam structure substantially different from the other benzodiazepine drugs considered for testing -"Old" chemical approved for use prior to FDA requirement for carcinogenicity testing and no longer under patent; hence FDA cannot require industry to test.
5. Oxazepam (604-75-1)	-Carcinogenicity in mice Prechronic studies should include sperm morphology testing. -Fertility assessment by continuous breeding (Moderate-High)	3,4	-Extensive use and human exposure -Metabolite of a number of benzodiazepine drugs -Lack of adequate carcinogenicity data in mice -"Old" chemical approved for use prior to FDA requirement for carcinogenicity testing and no longer under patent; hence FDA cannot require industry to test. -Develop data on structure-activity relationships for benzodiazepine drugs

TABLE 29 (Continued)

Chemical (CAS Number)	Testing Recommendation (Priority)	Chemical Selection Principles	Rationale/Remarks
B. Aminophenols			
1. o-Aminophenol (99-55-6)	No testing	--	-Limited human exposure -Little evidence of dermal absorption -Decreased interest in testing by nominator, because chemical is being replaced by methylaminophenol
2. p-Aminophenol (123-30-8)	No testing	--	-Limited human exposure -Decreased interest in testing by nominator, because chemical is being replaced by methylaminophenol
C. Other			
1. Chlorinated paraffins (C_{12}, 60% chlorine)	Defer	--	-Deferred pending EPA evaluation of industry studies on the *in vitro* absorption of the chemical through human skin

TABLE 30

TESTING RECOMMENDATIONS FOR CHEMICALS REVIEWED BY THE NTP BOARD OF SCIENTIFIC COUNSELORS ON OCTOBER 30, 1985

Chemical (CAS Number)	Testing Recommendation (Priority)	Rationale/Remarks
A. Chemicals Reviewed by CEC on February 5, 1985		
Wood Chemicals		
1. Ellagic acid (476-66-4)	No testing	-Limited exposure
2. Alpha-Terpineol (98-55-5)	Defer	-Defer until completion of NTP carcinogenicity study on delta-limonene, a structural analogue. -Review alpha-terpineol as part of a class study on structurally related terpenes tested by NTP.
B. Chemicals Reviewed by CEC on July 30, 1985		
Glycol ethers and Glycol ether acetates		
1. 2-Butoxyethanol acetate (112-07-2)	-Comparative *in vitro* esterase activities of ethylene glycol ether acetates -Genotoxicity studies (--)	-Potential for human exposure -Ascertain extent to which the ethylene glycol ether acetates are hydrolyzed to the parent glycol ethers

TABLE 30 (Continued)

Chemical (CAS Number)	Testing Recommendation (Priority)	Rationale/Remarks
2. 2-Ethoxyethanol (110-80-5)	-Comparative *in vitro* chemical disposition study of this compound and its acetate -Toxicity and carcinogenicity studies by inhalation route, including testing for hematological, immunological, and neurological effects (High)	-High production -Potential for increased usage -Known reproductive toxicity in animals
3. 2-Ethoxyethanol acetate (111-15-9)	-Comparative *in vitro* chemical disposition study of this compound and its parent glycol ether -Comparative *in vitro* esterase activities of ethylene glycol ether acetates -Genotoxicity studies (--)	-Potential for human exposure -Ascertain extent to which the ethylene glycol ether acetates are hydrolyzed to the parent glycol ethers
4. 2-Methoxyethanol (109-86-4)	-Toxicity and carcinogenicity studies by inhalation route (High)	-High production -Significant worker exposure -Lack of carcinogenicity data
5. 2-Methoxyethanol acetate (110-49-6)	-Comparative *in vitro* esterase activities of ethylene glycol ether acetates -Genotoxicity studies (--)	-Potential for human exposure -Ascertain extent to which the ethylene glycol ether acetates are hydrolyzed to the parent glycol ethers

TABLE 31

TESTING RECOMMENDATIONS FOR CHEMICALS REVIEWED BY THE NTP BOARD OF SCIENTIFIC COUNSELORS ON MARCH 25, 1986

Chemical (CAS Number)	Testing Recommendation (Priority)	Rationale/Remarks
A. Chemicals Reviewed by the Chemical Evaluation Committee on October 23, 1985		
1. n-Butyl acrylate (141-32-2)	-Chemical disposition studies by inhalation and dermal routes (Moderate) -Carcinogenicity in mice by inhalation route -Reproductive studies (Low)	-High production -Potential for worker exposure -EPA regulatory interest
2. 12-O-Hexadecanoyl-16-hydroxyphorbol-13-acetate (53202-98-5)	No testing	-Lack of evidence for exposure
3. Methyl ethyl ketoxime (96-29-7)	-In-depth toxicological evaluation to include behavioral studies by inhalation route -In vitro cytogenetics (Low)	-Potential for worker exposure
4. Alpha-Methylstyrene (98-83-9)	-In-depth toxicological evaluation -Short term *in vivo* reproductive toxicity assay -In vitro cytogenetics (Low)	-High production -Lack of toxicity data

TABLE 31 (Continued)

Chemical (CAS Number)	Testing Recommendation (Priority)	Rationale/Remarks
5. Tung oil (8001-20-5)	No testing	-Nomination is based on concern that 12-O-hexadecanoyl-16-hydroxyphorbol-13-acetate (HHPA) is a tumor promoter and a constituent of tung oil. However, no evidence that HHPA is a constituent of commercially available tung oil.
B. Chemicals Reviewed by the Chemical Evaluation Committee on January 8, 1986		
1. n-Butane (106-97-8)	Defer	-Reconsider after evaluation of data from industry subchronic studies in rats, and completion of NTP mutagenicity studies.
2. Catechol (120-80-9)	No testing	-Nominated to complete class study of hydroxybenzenes. However, sufficient data to characterize the toxicity of this class should be obtained from the current NTP testing of other hydroxybenzenes. -Information on catechol is expected from the metabolism on benzene.
3. 2-Chloronitrobenzene (88-73-3) 4. 4-Chloronitrobenzene (100-00-5)	-Prechronic studies - subchronic to include testing for hematopoietic and cardiac effects -Reproductive studies (High)	-Potential for exposure -Known toxicity -Positive mutagenicity data -Suspicion of carcinogenicity in limited animal studies -Concern about lack of reproductive toxicity data -Reviews results of subchronic studies regarding advisability of carcinogenicity studies for one or both isomers. -Structural activity relationship between isomers-review 3-chloronitrobenzene as a potential nomination to complete class study of chloronitrobenzenes.

TABLE 31 (Continued)

Chemical (CAS Number)	Testing Recommendation (Priority)	Rationale/Remarks
5. Furan (110-00-9)	-Chemical disposition and metabolism studies, including assessment of covalent binding -*In vivo* bone marrow cytogenetics -Unscheduled DNA synthesis (High)	-Significant commercial compound -Chemical carcinogenic in NTP studies -Look at potential for *in vivo* genotoxicity
6. Furfuryl alcohol (98-00-0)	-Carcinogenicity study in rats by oral route -Chemical disposition and metabolism studies -Genotoxicity studies (Moderate)	-Potential for exposure -Structural interest -Differential toxicities of furan, furfural and furfuryl alcohol in NTP prechronic studies -Chemical disposition and metabolism, and genotoxicity studies should precede carcinogenicity study.
7. Isopentane (78-78-4)	Defer	-Reconsider after evaluation of data from industry subchronic studies in rats.
8. Pentamidine isethionate (140-64-7)	Defer	-Deferred in order to contact Orphan Drug Review Board to ascertain if NTP toxicological testing would be appropriate.

TABLE 32

NTP FISCAL YEAR 1986 PRIORITY CHEMICALS FOR IN-DEPTH TOXICOLOGICAL EVALUATION

	Chemical	CAS Number
1.	t-Butylhydroquinone	1948-33-0
2.	2-Chloronitrobenzene	88-73-3
3.	4-Chloronitrobenzene	100-00-5
4.	Emodin	518-82-1
5.	2-Ethoxyethanol	110-80-5
6.	Furfuryl alcohol	98-00-0
7.	2-Methoxyethanol	109-86-4
8.	Styrene	100-42-5

CHEMICAL AND LABORATORY MANAGEMENT

Chemical Managers -- Once a chemical has been selected for study and referred to a particular program area, an NTP staff person -- designated the Chemical Manager -- is given the responsibility to ensure that the chemical receives a complete scientific evaluation. The Chemical Manager guides the chemical through each of the various study phases and has the responsibility to: (1) know and understand the relevant scientific literature; (2) present a protocol designed to measure relevant endpoints to the Toxicology Design Review Committee; (3) participate in the selection of a contractor for performance; (4) monitor the experiment's progress and maintain current awareness of the literature for this and structurally related chemicals; (5) provide liaison with groups doing other studies on the chemical; (6) evaluate the data; (7) write the toxicology and carcinogenesis technical report; (8) present the technical report first to the internal peer review group and then to the Board of Scientific Counselors' Peer Review Panel; (9) prepare the final technical report and journal articles after Peer Review Panel approval; (10) respond to appropriate requests for information on that chemical; and (11) review the data audit on the chemical. The Chemical Manager also maintains a liaison with the nominators of the chemical, with the industry that manufactures or uses the chemical, and with appropriate governmental agencies that have a regulatory interest. (CONTACT PERSON: Dr. J. Selkirk)

As an adjunct, the Pathology Working Group, the Data Analysis Group, and the Quality Assurance Group perform quality control functions. These groups ensure that: (1) an independent pathology laboratory examines slides from all target organs and tissues and 10 percent of all others; (2) studies are designed properly with regard to statistical requirements, and (3) the technical reports accurately reflect the data found.

Project Officers -- These are NTP staff scientists who are responsible for monitoring and evaluating the overall operation of the laboratories performing toxicology and carcinogenesis studies for the NTP in accordance with the standards and practices set forth in the NTP General Statement of Work. To establish that the studies are well conducted (scientifically, cost-efficient, and timely), these scientists initiate: (1) annual program reviews by peer groups of scientists; (2) quarterly site visits; (3) *ad hoc* visits by chemical managers and experts in various scientific disciplines as needed; (4) communication with the laboratory principal investigator and relevant NTP personnel; and (5) interaction with NTP contract specialists. These project officers/scientists are the Program's official representatives in all dealings with the laboratories performing the toxicology studies. (CONTACT PERSON: Dr. J. Selkirk)

QUALITY ASSURANCE PROGRAM

During FY 1986, quality assurance (QA) within the TRTP was expanded from a single position to a group of three professionals to better meet the needs of the program. During FY 1987, two additional professionals will be added to the group so that broad experience and expertise is available in the areas of toxicology, chemistry, histopathology, and related disciplines.

The primary activities of the QA Group can be outlined as follows: (1) interact with NTP discipline leaders and participate in annual program reviews to assure quality conduct and documentation of toxicology and carcinogenicity studies performed at master agreement contract laboratories, (2) conduct GLP inspections at all contract laboratories to assure that NTP studies are performed in compliance with (or in the spirit of, as specified by each contract) Good Laboratory Practice (GLP) regulations, (3) perform audits of studies in progress for all studies that are included in NTP Technical Reports, and (4) perform retrospective data audits of completed, long-term studies and audits of Board Draft NTP Technical Reports. These and other activities are carried out both by the QA group members functioning as a team and through supervision of QA support contracts (three each for performing retrospective audits and GLP inspections at laboratories plus audits of studies in-progress). (CONTACT PERSON: Dr. D. Bristol).

GLP Compliance Inspections And Audits -- The NTP has conducted GLP compliance inspections and audits of studies in progress at the master agreement contract laboratories since 1982. During FY 1986 this program was intensified and expanded to include study conduct inspections and audits of chemistry, pathology, as well as toxicology data at the master agreement laboratories, pathology support contractors and all testing laboratories which produced data in the fields of immunology, pharmacokinetics, teratology, fertility assessment, and animal health serological screening tests that may be incorporated in the Technical Reports. These inspections and audits are performed to assure quality study conduct and data collection in compliance with the NTP General Statement of Work, the study protocol, standard operating procedures (SOPs) for the testing facility and for compliance with the Food and Drug Administration Good Laboratory Practice (GLP) regulations. These audits and inspections for quality of performance and data covered 38 separate site visits during FY 1986. Some of these laboratories conduct activities classified as research, methods development, or validation and thus do not come under the strict requirements for GLP compliance; however, the NTP has required these activities be carried out in the "spirit of GLPs." This is interpreted to mean that SOPs for general procedures will be written and followed, instrumentation will be calibrated and maintained, reagents, etc., will meet the high standards required under GLPs and the data will be complete and provide an adequate data trail to allow reconstruction of the conduct of the study. The reports will be reviewed by quality control and quality assurance procedures to assure that the data support the conclusions. The GLP regulatory requirement that inspections and audits be conducted by an on-site quality assurance unit (QAU) is not enforced; however, it is recommended that there be some interaction of the scientists and the QAU at the contractor laboratory.

In order to continue the NTP program of GLP compliance inspections and audits of studies in progress and to assure that there is no conflict of interest between the testing facilities and the auditors/inspectors, three new NTP - QA/GLP support service contracts will be awarded at the beginning of FY 1987. (CONTACT PERSON: Dr. C. Whitmire, NIEHS)

Data And Report Audits -- Data audits are integral to maintaining the high standards of quality assurance as conducted under the Toxicology Research and Testing Program (NIEHS/NTP). Because the results and conclusions in the NTP Technical Reports impact on public health issues relating to chemical toxicity and carcinogenicity, the data must be validated. Technical Reports are not brought to peer review and published until the data have been audited and the technical report validated. Experimental data derived from toxicology and carcinogenesis studies are audited retrospectively for completeness, consistency, and accuracy and to determine if experimental procedures are consistent with Good Laboratory Practices.

Since data audits were implemented in FY 1983, and through FY 1986 (September 30, 1986), 114 two-year toxicology and carcinogenesis studies conducted at 13 different testing laboratories have been audited. The laboratories where studies were performed that have been audited are: (1) Battelle Columbus; (2) Battelle Pacific Northwest; (3) EG and G Mason Research Institute; (4) Frederick Cancer Research Facility; (5) Gulf South Research Institute; (6) Hazleton Laboratories America; (7) Hazleton Laboratories, Government Services; (8) Microbiological Associates; (9) Papanicolaou Cancer Research Institute; (10) Physiological Research Laboratory; (11) Southern Research Institute; (12) Springborn Institute for Bioresearch, Inc.; and (13) IIT Research Institute.

During FY 1986 three new QA support contracts were added to the NTP resources. This allowed NTP to audit all outstanding reports which have been published but not released and those reports which have been peer reviewed but not published; a total of 49 full data audits were conducted (Table 33). During FY 1987 it is anticipated that all the studies at Gulf South Research Institute which have not been published can also be audited and a determination made regarding the preparation of technical reports. Also, a number of audits were performed that various agencies represented on the NTP Executive Committee's Subcommittee on Data Audits had requested. During FY 1987 the first order of priority will remain those studies ready for technical report preparation. The second priority will be to evaluate and interpret the audit findings on individual studies and groups of studies so that the backlog of results can be published using appropriate channels.

During FY 1986, the inspection of pathology materials (wet tissues, blocks, and slides) was moved up in time to follow their receipt at the NTP Archives. This change provides for the earlier identification of potential discrepancies (when they exist) so that they can be addressed and resolved before the quality of pathologic diagnoses for a study are assessed by a pathology working group (PWG). The responsibility for performing this inspection was transferred from pathology to QA support contractors in order to eliminate a duplication of effort, since the inspection of pathology materials no longer needs to be included as part of the QA data audit conducted following completion of the PWG for a study. (CONTACT PERSON: Dr. D. Bristol, NIEHS).

Other Quality Maintenance Procedures -- The conference Managing Conduct and Data Quality of Toxicology Studies was planned and conducted (November 18-20, 1985) by representatives of the NTP and the American Industrial Health Council (AIHC). The conference was well attended with over 600 participants and approximately ten percent of the attendees were foreign representatives. The papers presented at this conference and the audience participation in discussions were published as a book (Princeton Scientific Publishing Co., Inc.) in May 1986. The book also presents topics that could be used in future conferences which bring industry and government together to address mutual concerns in toxicological testing. (CONTACT PERSONS: Drs. C. Whitmire and D. Bristol, NIEHS)

Another phase of NTP's efforts on maintenance of quality at the contract toxicology facilities consists of audits performed during the course of studies and participation in the program reviews by the various discipline leaders. Good Laboratory Practice (GLP) compliance is only the baseline for assuring quality. The QA/GLP discipline leader is responsible for evaluating the presence of an effective Quality Assurance Unit (QAU) at each laboratory. The interaction of this unit with NTP contract activities and facility management places emphasis on quality. The NIEHS has agreements with GLP regulatory compliance groups at both the FDA and the EPA to share audit and inspection findings. There is also close cooperation between the NTP and the Army for the activities at laboratory facilities that are common to both groups. In addition, joint monitoring of NTP/NIOSH contracts is carried out related to GLP compliance programs. (CONTACT PERSON: Dr. C. Whitmire, NIEHS)

In order to standardize and establish the best possible approach to in-life inspections and audits and retrospective audits, standard operating procedures (SOPs) have been prepared related to these activities. Such approaches are continuously being improved with these SOPs being regularly reviewed and revised. (CONTACT PERSONS: Dr. C. Whitmire, NIEHS)

The members of the NTP Quality Assurance unit are active members in the Society of Quality Assurance (SQA) and participate in the SQA education committee which is planning a training program at the October 1986 Society meeting in Chicago. (CONTACT PERSON: Dr. C. Whitmire, NIEHS)

NIOSH

The NIOSH Division of Biomedical and Behavioral Science has a Good Research Practices program under which all of its research is conducted. The program includes a QA unit, written SOPs and archives. The QA unit reviews protocols, and audits records and research in process. (CONTACT PERSON: Dr. R. Mason, NIOSH)

TABLE 33

DATA AUDITS CONDUCTED IN FY 1986

CHEMICAL	CAS NUMBER	SPECIES*	ROUTE**
Allyl Isothiocyanate	57-06-7	RM	GAV
Allyl Isovalerate	2835-39-4	RM	GAV
2-Amino-5-Nitrophenol	121-88-0	RM	SP
Asbestos, Amosite	12172-73-5	R	FEED
Asbestos, Amosite	12172-73-5	H	FEED
Asbestos, Chrysotile(IR)	12001-29-5	H	FEED
Asbestos, Chrysotile(SR)	12001-29-5	H	FEED
Asbestos, Chrysotile(IR) + Dimethyl Hydrazi	12001-29-5	H	FEED
Bisphenol A	80-05-7	RM	FEED
Boric Acid	10043-35-3	M	FEED
Bromodichloromethane	75-27-4	RM	GAV
Castor Oil	8001-79-4	RM	FEED
Chloropheniramine Maleate	113-92-8	RM	GAV
C.I Acid Orange 3	6373-74-6	RM	GAV
C.I. Acid Red 14	3567-69-9	RM	FEED
C.I. Acid Yellow 73 (Fluorescein Sodium)	518-47-8	RM	WATER
Coconut Diethanolamide	68603-42-9	RM	SP
1,4-Dichlorobenzene (P-Dichlorobenzene)	106-46-7	RM	GAV
Dichloromethane (Methylene Chloride)	75-09-2	RM	GAV
Dimethyl Methylphosphonate	756-79-6	RM	GAV
1,2-Epoxybutane	106-88-7	RM	INHAL
Ethylene Glycol Monoethyl Ether (EGMEE)	110-80-5	RM	GAV
Ethylene Oxide	75-21-8	M	INHAL
FD and C Yellow No. 6	2783-94-0	RM	FEED
Gilsonite	12002-43-6	RM	FEED
Gum Arabic	9000-01-5	RM	FEED
Hamamelis Water (Witch Hazel)	68916-39-2	RM	SP
1,2,3,6,7,8-Hexachlorodibenzo-p-dioxin	57653-85-7	RM	GAV
Hexylresorcinol	136-77-6	RM	GAV
Locust Bean Gum	9000-40-2	RM	FEED
Malonaldehyde, Sodium Salt	24382-04-5	RM	GAV
Mercaptobenzothiazole	149-30-4	RM	GAV
Methyl Carbamate	598-55-0	RM	GAV
Methyl Ethyl Ketone Peroxide	1338-23-4	RM	SP
Nitrofurantoin	67-20-9	RM	FEED
Pentachloronitrobenzene	82-68-8	M	FEED
Pentachloroethane	76-01-7	RM	GAV
N-Phenyl-2-Napthylamine	135-88-6	RM	FEED
Pyridine	110-86-1	RM	GAV
Rotenone	83-79-4	RM	FEED
Sodium Dodecyl Sulfate	151-21-3	RM	FEED
Stannous Chloride	7772-99-8	RM	FEED
2,3,7,8-Tetrachlorodibenzo-p-dioxin	1746-01-6	RM	GAV
2,3,7,8-Tetrachlorodibenzo-p-dioxin	1746-01-6	R	SP

1,1,1,2-Tetrachloroethane	630-20-6	RM	GAV
Tetrachloroethylene	127-18-4	R	GAV
Tetrachloroethylene	127-18-4	R	GAV
Tetrachloroethylene	127-18-4	R	GAV
Tetrachloroethylene	127-18-4	R	GAV
Tetrachloroethylene	127-18-4	M	GAV
Tetrakis(hydroxymethyl)Phosphonium Chloride	124-64-1	RM	GAV
1,1,1-Trichloroethane (Methyl Chloroform)	71-55-6	RM	GAV
Vinylidene Chloride	75-35-4	RM	GAV
Xylene, Commercial Mixture	1330-20-7	RM	GAV
2,6-Xylidine	87-62-7	R	FEED
Zearalenone	17924-92-4	RM	FEED
Ziram	137-30-4	RM	FEED

*R = Rats
M = Mice
H = Hamsters

** FEED = Oral in food
GAV = Gavage
INHAL = Inhalation
SP = Skin paint
WATER = Oral in water

CHEMISTRY RESOURCES

The chemistry program serves as a central resource for all study and research activities of the NTP. Maintained to assure chemical quality and to minimize testing results variability due to external sources, the chemistry needs are facilitated via integrated contract mechanisms, an active in-house laboratory, and cooperation and interaction with other NTP operations. The chemistry capabilities provide for procurement, chemical analysis, analytical methods development, purification and/or synthesis of test chemicals and tissue residue analysis.

FY 1986 ACCOMPLISHMENTS

The analytical services support contracts continued to very actively support a large number of NTP programs. As in the past, the majority of the work was in support of the toxicology and carcinogenesis studies program. Eighty-eight chemicals were procured and/or analyzed.

The chemistry performed at the contract animal study laboratories is constantly monitored via review of the monthly reports received from the laboratories and annual chemistry discipline site visits to all testing laboratories. In some instances, it has been necessary to visit a laboratory more than the regular annual visit to address chemistry related problems associated with the toxicity studies.

During FY 1986, 12 new chemicals were obtained for NTP teratology studies (Table 34) and analyzed including complete bulk chemical purity and identity assays, methods development for bulk chemical stability, as well as dosage formulation, stability and concentration assay methods. Information generated was provided to the teratology program leaders and the contract laboratories. Also, technical input in the area of chemistry and dose preparation was given to the teratology program by means of site visits to the teratology contract laboratories.

The chemistry resource continued support of the NIEHS reproductive toxicology's continuous breeding program. Nine chemicals were obtained (Table 35) for study in this program and distributed to the contract laboratories. These chemicals were procured and/or analyzed in a similar manner to those obtained for the teratology program.

The chemistry resource also continued support of the NTP's immunology program contract research by providing analytical chemistry services for the twelve chemicals currently on study under this initiative (Table 36). Services provided were analogous to those provided for the continuous breeding program and also included methods development and analysis of tissues for test chemical residues.

The chemistry resource continued support of the short-term _in vivo_ rat liver model program contract initiative (Table 37).

During FY 1986 the chemistry resource continued its support for all chemicals studied by the TRTP's Cellular and Genetic Toxicology Program. This support includes an initial chemical screening assay for purity and identity for all chemicals identified for study in the program. A total of 115 chemicals were analyzed in FY 1986. In addition a more comprehensive chemical analysis to identify major impurities was carried out on selected chemicals.

Continued support was provided to several NTP/TRTP investigators in the areas of chemical synthesis, tissues residue analysis and bulk chemical purity and dose mixture concentrations verification (Table 38). During FY 1986, tissue and body fluid residue analyses included samples from chronic toxicity studies of arsine, a subchronic toxicity study of methylisocyanate and a reproductive toxicology study of di(2-ethylhexyl)phthalate.

During FY 1986, the chemistry resource continued research into the possibility of microencapsulation as an alternative vehicle for administration of test chemical in the feed. Several chemicals including trichloroethylene, citral, 1,1,1-trichloroethane and 2-ethylhexanol were encapsulated. Studies, including physical and chemical stability of the encapsulated material and/or feed mixes as well as bioavailability of encapsulated material were carried out. In addition, the TRTP chemistry resource laboratory continued support of several in-house studies (Table 39). A simple method for the detection of NPPD ("Spy Dust") was developed in the chemistry resource laboratory.

The data audit program has received significant support through the chemistry program. Procedures for auditing the chemistry performed at the study laboratories have been developed and applied to both a prospective and retrospective review of toxicity studies. The chemistry program was also an active participant in the organization and running of the Symposium for Managing Conduct and Data Quality of Toxicology Studies held in FY 1986. (CONTACT PERSONS: Dr. C.W. Jameson and Dr. T.J. Goehl, NIEHS)

FY 1987 PROGRAM PLANS

During FY 1987, the chemistry resource will continue to support the toxicology and carcinogenesis studies program by procuring and analyzing all new study chemicals. The chemistry resource will also continue to support the cellular and genetic toxicology, teratology, reproductive toxicology, immunology, and the short-term in vivo rat liver tumor model programs.

Collaboration with in-house TRTP investigators will be continued through the in-house chemistry resource laboratory and the local chemistry services support contract laboratory. Research activities to investigate the suitability of microencapsulation as an alternative vehicle for administration of test chemicals will continue to be actively pursued. (CONTACT PERSONS: Dr. C. W. Jameson and Dr. T.J. Goehl, NIEHS)

TABLE 34

CHEMICALS PROCURED AND ANALYZED IN FY 1986 FOR TERATOLOGY STUDIES

CHEMICAL	CAS Number
Acetone (Inhalation)	67-64-1
Butyl benzyl phthalate	85-68-7
Diethylene glycol diethyl ether	112-36-7
Diethyl phthalate	84-66-2
Dimethyl phthalate	131-11-3
Ethylene glycol diethyl ether	629-14-1
2-Ethylhexanol	104-76-7
Hexachloro-1,3-butadiene	87-68-3
N-Hexane (Inhalation)	110-54-3
Mono(2-ethylhexyl)phthalate	4376-20-9
Tetrahydrofuran (Inhalation)	109-99-9
1,1,1-Trichloroethane (Methyl chloroform)	71-55-6

TABLE 35

CHEMICALS PROCURED AND ANALYZED IN FY 1986 FOR CONTINUOUS BREEDING PROGRAM

CHEMICAL	CAS Number
Acrylamide	79-06-1
Aniline hydrochloride	142-04-1
Bromoform	75-25-2
Chloroform	67-66-3
Ethylene glycol monomethyl ether	109-86-4
2-Ethylhexanol	104-76-7
Mono(2-ethylhexyl)phthalate	4376-20-9
Nitrofurantoin	67-20-9
4-Vinylcyclohexane	100-40-3

TABLE 36

CHEMICALS PROCURED AND/OR ANALYZED IN FY 1986 FOR IMMUNOTOXICOLOGY STUDIES

CHEMICAL	CAS Number
Arsenic Trioxide	1327-53-3
Cobalt Sulfate Heptahydrate	10026-24-1
4-Chloro-o-phenylenediamine	95-83-0
2,4-Diaminotoluene	95-80-7
Gallium Arsenide	1303-00-0
Gallium (III) Oxide	12024-21-4
Gallium Nitrate Hydrate	13494-90-1
Lithium Carbonate	554-13-2
p-Nitrotoluene	99-99-0
Sodium Arsenite	7784-46-5
2,3,7,8-Tetrachlorodibenzo-p-dioxin	1746-01-6
Tetraethyl Lead	78-00-2

TABLE 37

CHEMICALS PROCURED AND ANALYZED IN FY 1986 FOR RAT LIVER TUMOR MODEL

CHEMICAL	CAS Number
Acetaminophen (4-hydroxyacetanilide)	103-90-2
1-Amino-2,4-dibromoanthraquinone	81-49-2
Chlorendic acid	115-28-6
C. I. Solvent Yellow 14	842-07-9
Monuron	150-68-5
4,4'-Oxydianiline	101-80-4

TABLE 38

CHEMISTRY RESOURCE SUPPORT FOR TRTP IN-HOUSE STUDIES IN FY 1986

CHEMICAL (CAS No.)	Type of Study	Analysis Performed
Aflatoxin (1402-18-2)	Comparative Toxicology	Dose formulation and analysis
Arsine (7784-42-1)	Comparative Toxicology	Tissue Residue analysis
Carisoprodol (78-44-4)	Comparative Toxicology	Dose formulation and analysis
Chloroform and (67-66-3) Hexachlorobutadiene (87-68-3)	Chemical Mixture Study	Purity analysis, dose formulation stability and analysis
Cimetidine	Reproductive Toxicology	Purity analysis, dose formulation stability and analysis
Di(2-ethylhexyl)phthalate (117-81-7)	Reproductive Toxicology	Dose formulation and analysis, analyze animal tissue for ZN
Diethylnitrosamine (55-18-5)	Comparative Toxicology	Dose formulation and analysis
Diethylstilbestrol (56-53-1)	Comparative Toxicology	Dose formulation and analysis
Disperse Blue 1 (2475-45-8)	Mutagenicity	Chemical purification
2-Ethoxyethanol (110-80-5)	Comparative Toxicology	Purity analysis, dose formulation stability and analysis
Gallium Arsenide (1303-00-0)	Comparative Toxicology	Dose formulation stability and analysis Tissue residue analysis
Hexachlorobenzene (118-74-1)	Comparative Toxicology	Purity analysis, dose formulation and analysis, tissue residue analysis

TABLE 38 (Continued)

1,2,3,4,7,8-Hexachlorodibenzofuran	Comparative Toxicology	Dose analysis
Mercaptobenzimidazol (583-39-1)	Immunology	Dose formulation and analysis
Methyl bromide (74-83-9)	Comparative Toxicology	Purity, dose formulation and analysis
Nickel Sulfate (10101-97-0)	Comparative Toxicology	Dose formulation and analysis and tissue residue analysis
Nicotine precursors	Oncogene Study	Synthesis
2,3,4,7,8-Pentachlorodibenzofuran	Comparative Toxicology	Dose analysis
Pyridine (110-86-1)	Comparative Toxicology	Purity analysis, dose formulation stability and analysis
4,4'-Thiobis(6-t-butyl-m-cresol) (96-69-5)	Comparative Toxicology	Dose formulation and analysis

TABLE 39

TRTP CHEMISTRY LABORATORY STUDIES

IN FY 1986

CHEMICAL (CAS No.)	Type of Study	Analysis Method
1,3-Butadiene (106-99-0)	Chemical purity analysis	Gas chromatography with flame ionization detection
Carbohydrates	Isolation and identification of unknown carbohydrates in Sertoli cell tissue culture	High performance liquid chromatography with refractive index detection
CoA-thioesters	Synthesis and purification by paper chromatography	U.V. spectroscopy
Cyanide	Blood level determination in rats exposed to methylisocyanate	Visible sectroscopy
2-Ethoxyethanol (110-80-5)	Bioavailability of microencapsulated material	Gas chromatography with flame ionization detection
2,5-Hexanedione	Isolution and quantitation in sertoli cell tissue culture	Gas chromatography with flame ionization detection
Hydroxycoumarin	Determination of extent of metabolism of ethoxycoumarin by liver and kidney homogenetic	High performance liquid chromatography with fluorescence detection
Methyl bromide (74-83-9)	Dosage confirmation in peanut oil vehicle	Gas chromatography with flame ionization detection
5-(4-Nitrophenyl)-2,4-pentadien-1-al (2608-48-2)	Chemical characterization and detection method	Color reaction and High Performance Liquid Chromatography
Ochratoxin A (303-47-9)	Dose confirmation in saline	High Performance Liquid Chromatography
Peptide Ligands	Fourier transform/ Infrared spectroscopy	Confirmation of Structure

CHEMICAL HEALTH AND SAFETY RESOURCES

Toxicological characterization of environmental chemicals often involves potentially hazardous materials from both the acute and chronic standpoint. Such a program must protect both the worker and the environment, conform to guidelines and regulations and help ensure the integrity of the study. Included in the maintenance of an NTP program specific, state-of-the-art, chemical health and safety effort are the following: chemical monitoring and industrial hygiene surveys; periodic review of training needs; and formulation of standards, guidelines and safety plans. Chemical health and safety coverage also includes the receipt, storage, shipment and handling of test chemicals by a chemical repository. In addition, the NTP Chemical Health and Safety Section advises and serves as an informational resource for in-house TRTP efforts.

The NTP Chemical Repository provides repository and safety support to all branches of TRTP. It provides a mechanism whereby approximately 200 test chemicals per year are located, procured, analyzed for physical properties, archived and distributed in a manner which ensures their safe handling, chemical integrity and maintains confidentiality of identity when necessary. The Chemical Repository searches through on-line computer data bases to produce chemical specific safety documents both for day-to-day safe handling of the compounds as well as for emergency situations. Chemicals, for which flash point, vapor pressure or density are unavailable in the literature, are analyzed and the physical properties are determined. Upon completion of the animal studies, the Chemical Repository receives and aliquots an archive sample of the test chemical, then arranges for the environmentally safe disposal of the surplus chemical. Thus, the Chemical Repository, as part of Chemical Health and Safety Resources, is involved in the entire toxicology testing cycle.

FY 1986 ACCOMPLISHMENTS

The scope of NTP Chemical Health and Safety Resources includes four types of activities: 1) tracking and monitoring; 2) chemical-specific health and safety documents; 3) technical assessment and control; and 4) Chemical Repository and safety support.

Tracking and Monitoring -- Program accomplishments in the area of tracking and monitoring for FY 1986 include the establishment of a basic level of safety awareness at the NTP contractor laboratories and a continuation in the site visit program at a maintenance level. Health and Safety visits were conducted at two chemistry support contract laboratories, six systemic toxicology contract laboratories, one cellular and genetic toxicology laboratory and eight Master Agreement laboratories. A visit to the NTP Pathology Repository and Archives resolved several ventilation problems and clarified formaldehyde handling concerns. Minimum Requirements for Health and Safety, which are part of all TRTP sponsored laboratory work, were reviewed and revised. This revision reflects the experience and development of the laboratories working under the original Health and Safety Minimum Requirements which were introduced several years ago. A draft of the NTP Health and Safety Manual is in progress. This document is being prepared to assist Principal Investigators, Project Officers and others without professional chemical health and safety backgrounds to better understand NTP minimum requirements and the alternate approaches with which the requirements can be met. Other ongoing activities include: monitoring of Master Agreement laboratory monthly reports; maintenance of up-to-date laboratory site visit notebooks; monitoring of health and safety archive information at Master Agreement laboratories; and review and approval of Master Agreement laboratory Health and Safety Plans.

Chemical-Specific Health and Safety Packages -- Approximately 95 Health and Safety Packages were prepared during FY 1986 in an ongoing effort to provide chemical specific information during the protocol design and testing stages. In addition, Health and Safety Packages are prepared for all NTP Superfund chemicals.

Technical Assessment and Control -- Several projects have been undertaken in technical assessment and control to improve health and safety standards during toxicity testing operations. The design, installation and evaluation of a prototype tissue trimming work station has been completed. The prototype stations were placed in service in the in-house TRTP laboratories at the NIEHS facilities in Research Triangle Park, North Carolina. Validation has been completed of work previously performed in the areas of: 1) chemical tracer studies to assess contamination during common laboratory operations; (2) permeation of protective gloves by formalin; and 3) the design and testing of a vented enclosure for laboratory balances. The development and testing of a vented, portable dose administration station for *in vivo* laboratories has also been completed.

Repository and Safety Support -- The NTP Chemical Repository sent approximately 1300 aliquots to investigators during FY 1986, either as coded blind samples or as uncoded aliquots (Table 40). Dust explosion and lower and upper explosive limits were determined for potentially explosive inhalation test chemicals. Glove permeation data on non volatile test chemicals were determined by discrete sampling. Glove permeation testing procedures for gases, solids and solutions were also initiated. In FY 1986, the first radiolabeled substance was shipped from the Chemical Repository to a testing laboratory. Effluent waste water testing began at several contract laboratories in FY 1986. (CONTACT PERSON: Dr. D.B. Walters)

FY 1987 PROGRAM PLANS

Tracking and Monitoring -- The Chemical Health and Safety Resource staff will continue to inspect and monitor all current NTP laboratories on a periodic basis along with all new laboratories receiving awards and those current laboratories which have had significant facility modifications. In addition, Chemical Health and Safety will continue to participate in the yearly program reviews of all Master Agreement laboratories as well as monitor the monthly reports for compliance with Health and Safety Requirements. Work will be undertaken on the development and validation of a vented cage dumping station and also on the evaluation of effective dose preparation containment controls.

Chemical-Specific Health and Safety Packages -- Documents on safe handling of chemicals will be refined to provide more pertinent information for contract laboratories in an easy to read format in order to comply with the new Right-To-Know laws and the possible forthcoming OSHA Laboratory Standards.

Repository and Safety Support -- During FY 1987 the Chemical Repository and Safety Support program will continue to provide assistance to the TRTP and the NTP. Waste water monitoring will be completed in FY 1987. Glove permeation testing of gases, solids and solutions to be used in TRTP prechronic and chronic studies will be implemented in FY 1987. (CONTACT PERSON: Dr. D.B. Walters)

TABLE 40

NTP CHEMICAL REPOSITORY AND SAFETY SUPPORT HOLDINGS AND ACTIVITIES IN FY 1986

1.	Control chemicals in inventory	5
2.	Total number of unique chemicals	1746
3.	Test chemicals shipped for *Salmonella* testing in FY 1986	180
4.	Test chemicals shipped for *Drosophila* testing in FY 1986	41
5.	Test chemicals shipped for cytogenetics testing in FY 1986	120
6.	Test chemicals shipped for *Drosophila* aneuploidy testing in FY 1986	46
7.	Test chemicals shipped for yeast aneuploidy testing in FY 1986	80
8.	Test chemicals shipped for mouse lymphoma testing in FY 1986	75
9.	Test chemicals shipped for cellular and genetic toxicology testing other than 3,4,5,6,7,8 in FY 1986	299
10.	Aliquots shipped in FY 1986	1294
11.	Chemicals selected for FY 1986 *Salmonella* testing	252
12.	Chemicals selected for FY 1986 *Drosophila* testing	68
13.	Chemicals selected for FY 1986 cytogenetics testing	158

TABLE 40 (Continued)

14.	Number of flash point determinations	25
15.	Number of vapor pressure determinations	50
16.	Number of density determinations	25
17.	Number of stability determinations	70
18.	Number of solubility determinations	125
19.	Number of chemicals tested in glove permeability studies	34
20.	Number of bulk chemicals disposed	40

DATA MANAGEMENT AND ANALYSIS

NTP data management activities involve data processing and computer support for several of the NTP testing and methods development programs. They include management of support contracts which provide services such as data collection, computer programming and report generation, and in-house development of management and administrative information systems.

The NTP also receives statistical research support from the Statistics and Biomathematics Branch of the Biometry and Risk Assessment Program of the NIEHS. These research activities deal with various issues of experimental design, data analysis, and interpretation of results from NTP carcinogenicity and mutagenesis studies. Specific research problems are discussed in detail below.

NIEHS

FY 1986 ACCOMPLISHMENTS

- Data Processing Systems

CHEMTRACK -- Data base administration and software development continued on the CHEMTRACK management information system, which provides the NTP with an interactive chemical tracking, report generation, and ad hoc query system. Information for more than 2400 chemicals exists in CHEMTRACK, including chemical identification information, nomination/selection information and activities, milestone dates, test data and status information for the mutagenesis, carcinogenesis, immunology, chemical disposition and reproductive and developmental toxicology test programs and NTP publication information. Procedures were developed to allow NTP administrative and scientific personnel to query the CHEMTRACK files and generate workload reports and calendars. Data entry is performed interactively with each program element taking responsibility for updating its own data. The on-line component of CHEMTRACK resides on the Model 204 Data Base in the Parklawn Computer System. The major CHEMTRACK reports, including the Management Status Reports and NTP Results Reports, are generated by the in-house Vax 11/780 computer. (CONTACT PERSON: Mr. M. Rowley)

Development and Operation of a Computerized Data Management System for the Cellular and Genetic Toxicology Branch -- A database was prepared summarizing chemical data and the results of genetic toxicology and rodent carcinogenicity testing. The purpose of this database is to evaluate the short-term tests and their potential for predicting carcinogenesis. Salmonella, Drosophila, in vitro Chinese hamster ovary cytogenetics, and mouse lymphoma subsystems continued to collect and analyze experimental data and produce summaries for publication. The systems were enhanced with improved publication reports for Salmonella, evaluation and processing changes for cytogenetics, better methods for analyzing, summarizing, and evaluating mouse lymphoma data, and direct transmission of formatted data for inclusion in NTP Technical Reports. Requirements for a yeast aneuploidy subsystem were prepared, and programming has begun. Prototype yeast strain storage, tetrad analysis, and aneuploidy tracking subsystems were developed. (CONTACT PERSON: Mr. R. Minor)

Carcinogenesis Bioassay Data System (CBDS) -- Management support was provided for CBDS, which for fourteen years has supported the collection, computer storage, and processing of data from NTP carcinogenicity studies into tables for the NTP Technical Reports. The CBDS is being replaced by the Toxicology Data Management System (TDMS); however, because of the number of chemical studies, still in some phase of CBDS processing, the transition will not be completed for several years. Plans have been made to replace the existing CBDS contract with a smaller contract for this phase-out period. (CONTACT PERSON: Mr. M. Rowley)

Toxicology Data Management System (TDMS) -- In FY 1986, the TDMS was used for in-life data collection for chronic and prechronic tests. The micropathology system was used for interim and terminal sacrifices as well as early deaths for all chemicals supported by the in-life system. The conversion of TDMS to ADABAS has been divided into five phases, the first of which is complete. TDMS was used to process data for 118 chemicals. The NTP TDMS liaison function was transferred from NCTR to NIEHS in phases which ended on March 15. The software development and maintenance function will be transferred between August 1 and September 30, 1986. A study was completed which identified specifications for new microcomputers to be used in the NTP laboratories for data collection and processing. An investigation and evaluation of commercially available toxicology and pathology systems was completed. Detailed information on TDMS may be found in the NCTR entry of this section. (CONTACT PERSONS: Ms. N. Stegman and Mr. G. Nehls)

Data Management Systems for Prechronic Studies -- Data from completed NTP prechronic studies and special reproduction and fertility studies continued to be added to existing computerized data bases. At present, data from over 100 prechronic studies and 50 fertility assessments by continuous breeding experiments are maintained in these data management systems. Historical control summary information as well as data from individual studies can be extracted for organ and body weights, hematology, clinical chemistry, and reproduction and fertility parameters. Prechronic study data can be assessed and summarized by route of administration, laboratory, study date, animal supplier, and age of animals at study initiation. (CONTACT PERSONS: Mr. S. Seilkop and Dr. J. Haseman)

Statistical Software Development for TDMS -- Statistical software development activities for TDMS were directed mainly toward the completion of the tools necessary for the production of NTP Technical Reports. Minor modifications to existing software for statistical analysis of tumor incidence and survival rates were made and new software was developed to enhance TDMS statistical reporting capabilities. This included the ability to generate publication-ready tables containing descriptive statistics for weekly food, water, and compound consumption, body weights, and survival rates. In addition, software for producing camera ready plots of growth and survival curves was completed. (CONTACT PERSONS: Mr. S. Seilkop and Dr. J. Haseman)

• Statistical Studies

Many recent NTP toxicology and carcinogenesis studies have utilized a pathology evaluation protocol which reduces the amount of pathology required relative to earlier experiments. It is important to understand how this experimental design modification may affect the sensitivity of the study for detecting carcinogenic effects. Changes in the power and Type I error of the linear trend test in proportions were investigated in a simulation study which considered more than 300 possible dose-response relationships. It was found that the reduced pathology protocol had little impact on the probability of detecting a statistically significant result. (CONTACT PERSON: Dr. C. Portier)

Most current carcinogenesis studies only indicate whether or not a particular tumor is present at death, and do not provide information on cause of death for individual animals. Statistical methods were developed using stochastic models to describe the progression from tumor onset to death with a tumor. These methods do not require cause of death information. Using these methods, a semi-parametric analysis for tumor onset times was developed to test for dose-related increases in tumor incidence. This analysis uses a parametric distribution for the tumor onset times, but not for the death rates of tumor-bearing or tumor-free animals. (CONTACT PERSON: Dr. C. Portier)

The error rates of several survival-adjusted tests for a dose-related trend in the prevalence of non-lethal tumors were investigated. The various tests performed similarly when mortality patterns were the same across dose groups. When dose affected survival, however, the test based on a logistic regression model was more powerful than the usual age-stratified test, while still retaining a reasonable Type I error rate. (CONTACT PERSON: Dr. G. Dinse)

Estimators were derived for the age-specific prevalence and mortality functions, which are important descriptors of tumor development and the subsequent effect of the tumor on longevity. No assumptions were made about the degree of tumor lethality or the distribution of survival times. The proposed estimators incorporate sacrifice data and require information on the tumor's role in causing death for only a subset of the tumor-bearing animals. In fact, these methods allow cause of death to be classified into ordered categories according to how likely it was that the tumor was responsible for death. (CONTACT PERSON: Dr. G. Dinse)

Survival differences can have a substantial impact on the analysis of incidental tumors. Examples were developed to illustrate several of the advantages of basing the analysis on logistic regression rather than the usual age-stratified methods. Logistic regression allows a continuous adjustment for survival, is less susceptible to the bias or insensitivity that treatment toxicity can inflict on the age-stratified analysis, and can account for the effects of influential covariables. (CONTACT PERSONS: Dr. G. Dinse and Dr. J. Haseman)

Data from NTP carcinogenicity studies were examined to determine how the utilization of statistical analyses based on the proportion of animals with primary tumors (all sites) or the proportion of animals with malignant tumors (all sites) would have affected the interpretation of the data compared to analyses of site-specific effects. This evaluation revealed that fewer carcinogenic effects would have been detected by this approach. Two major problems are associated with an evaluation based on all-site tumor rates: (1) the pooling of various tumor types reduces study sensitivity for detecting chemically-related increases in site-specific tumor incidences, and (2) the biological relevance of combining the incidences of tumors of varying morphologies and topographies is questionable. (CONTACT PERSON: Dr. J. Haseman)

The influence of caloric intake and energy expenditure, as indicated by body weight changes, on tumor incidence was investigated. In NTP dosed-feed studies, reduced body weight was found to be associated with decreased incidences of benign mammary and pituitary tumors in female F344 rats; reduced body weight also appeared to be associated with decreased incidences of leukemia in male F344 rats. For B6C3F1 mice, no clear trends were evident. These results suggest that 10-20% reductions in body weight may result in substantive decreases in the incidences of certain endocrine system tumors in the female F344 rat. (CONTACT PERSONS: Dr. J. Haseman and Dr. W. Piegorsch)

Research efforts continued on the issue of assessing possible interactions among two or more chemical exposures. This is important both for regulating acceptable exposure levels and for understanding possible mechanisms of action. Various procedures for assessing interactive effects were evaluated under Finney's null model of simple independent action. Among the procedures considered, the W-method of Wahrendorf et al. (Biometrics, 37: 45-54, 1981) was shown to have acceptable size, yet greater power for assessing synergistic departures from the null model than competing procedures. (CONTACT PERSON: Dr. W. Piegorsch)

After an extensive review of experimental results from a multitude of laboratories participating in a World Health Organization/International Program on Chemical Safety (WHO/IPCS) collaborative study, methods of analysis have been devised for two of the four in vivo assays presently judged appropriate for routine screening, the mouse bone marrow micronucleus assay and the measurement of unscheduled DNA synthesis (UDS) in rat hepatocytes. The analysis included an assessment of sources of variability, investigation of the usefulness of historical control data, documentation of the sizeable strain/species/laboratory differences possible in control rates, and demonstration that statistical tests for trend are sensitive indicators of dose response. In addition, a simple, but potentially effective method of measuring the potency of assay results has been devised. Preliminary results from the application of this potency measure to the micronucleus and UDS data from the IPCS study are sufficiently encouraging to justify further study of this approach. (CONTACT PERSON: Dr. B. Margolin)

Computer programs implementing the formal NTP statistical analysis for Ames test data have been delivered to the NTP Salmonella assay contractors. Preliminary reports are very favorable; the laboratories have indicated the positive value of rapid statistical feedback on their experimental data, especially in planning repeat experiments (CONTACT PERSON: Dr. K. Risko)

FY 1987 PROGRAM PLANS

· Data Processing Systems

CHEMTRACK -- Future plans for CHEMTRACK include a complete redevelopment of the interactive query to provide easier and more direct access to data across files and to facilitate the generation of ad-hoc reports. New features of the MODEL 204 host language, which will be made available in FY 1987, will allow significant improvements to the performance of the data base. (CONTACT PERSON: Mr. M. Rowley)

Carcinogenesis Bioassay Data System (CBDS) -- Because of the transition to TDMS, the CBDS support will continue to decrease. At the present time there are approximately 50-60 NTP chemicals in the CBDS data base that will be processed into NTP Technical Reports. A data base management system which will incorporate both CBDS and TDMS pathology data will be developed in the future on the Vax 11/780 for interactive query and statistical analysis. (CONTACT PERSON: Mr. M. Rowley)

Toxicology Data Management System (TDMS) -- In FY 1987, the transition from NCTR to NIEHS for laboratory liaison, software development and maintenance, and operations will be complete. The NCTR mainframe computer system will be used until September 30, 1987. During FY 1987, the conversion of TDMS to ADABAS will be complete and the system will be transferred from an IBM 4341 at NCTR to a DEC VAX 8650 at NIEHS. A competitive procurement will be awarded for microcomputers to replace the Modcomps presently used in the laboratories. Rewriting the software to operate on these microcomputers will begin. NTP Technical Reports will be prepared on the first TDMS chemicals. (CONTACT PERSONS: Ms. N. Stegman and Mr. G. Nehls)

Data Management Support for Laboratory Animal Studies -- The current contract with Program Resources, Inc. to provide data processing and statistical support for NTP's pre-chronic, chronic, and certain "special studies" expired on July 31, 1986. However, a competitive procurement will be awarded before the end of FY 1986 that will continue this support for an additional 3-5 years.

· Statistical Studies

One area on which future research will focus is the survival-adjusted analysis of tumor incidence rates in the absence of information on cause of death. Various methods are being developed which parametrically model the tumor incidence function, but do not place restrictions on tumor lethality and require only a few sacrifice times. Competing risks need not act independently of the tumor of interest, and the possible dependence of the risk of death-with-tumor on the tumor onset time need not be specified. (CONTACT PERSONS: Dr. C. Portier and Dr. G. Dinse)

A comprehensive re-evaluation of the results of 314 NTP/NCI carcinogenicity studies is underway. The objective is to interpret, in a consistent manner, the results as given in the Technical Report's summary.

This compilation should be useful as a consistent evaluation of these data and as a data base for further investigations, such as assessments of inter-species correlation or evaluations of association between laboratory animal carcinogenicity studies and other toxicological findings. (CONTACT PERSON: Dr. J. Haseman)

In a major joint effort with the Cellular and Genetic Toxicology Branch, a database has been assembled that will permit study of the extent to which the basic NTP *in vitro* tests for genetic toxicity, i.e., *Salmonella*, mouse lymphoma, sister chromatid exchanges, and chromosome aberrations, are predictive of the results observed in the two-year rodent carcinogenicity assay. Results of this study will have major implications for the NTP and the field of genetic toxicology in general. (CONTACT PERSON: Dr. B. Margolin)

As a consequence of earlier work on trend tests for binomial and negative binomial data, a study has begun to compare alternative analyses for dose response when the data are beta-binomially distributed. A secondary issue being considered is a comparison of alternative methods to test for the presence of extra-binomial variation. (CONTACT PERSON: Dr. K. Risko)

NCTR

TOXICOLOGY DATA MANAGEMENT SYSTEMS

The Division of Toxicology Data Management Systems (TDMS) actively supports the NTP in several areas. During FY 1986, this support included:

- Site support (contract laboratories)
- Software development
- Software maintenance and enhancement
- Central computer facilities
- Other projects as defined by the NTP

FY 1986 ACCOMPLISHMENTS

During September 1985, NIEHS informed NCTR that they were initiating the process of establishing their own software support contract and, thus, would be eliminating that support aspect from the existing interagency agreement (IAG) effective October 1, 1986. Therefore, a major activity during FY 1986 was the transition of those support functions from NCTR to the NIEHS software support contractor. Center Computer Facility and Production Control Support will continue through FY 1987.

Site Support -- Listed below are the laboratories and the dates that the NCTR Liaison support was transferred to NIEHS:

Battelle Columbus Laboratories	03/15/86
Battelle Northwest Laboratories	03/15/86
Bioassay Systems	03/15/86
Brookhaven National Laboratories	02/03/86
E.G. and G. Mason Research	02/03/86
Hazleton Laboratories, America	03/15/86
International Research and Development Corporation	03/15/86
Litton Bionetics	03/15/85
Lovelace Inhalation Toxicology Research Institute	02/03/86
Microbiological Associates	02/03/86
Midwest Research Institute/ Pathology Associates, Inc.	02/03/86
Southern Research Institute	02/03/86

As of April 1, 1986, all NCTR Liaison support under the NIEHS/NCTR IAG was terminated. NCTR continued to provide experiment materials support (i.e., cage and CID card preparation and distribution) through FY 1986 for each NIEHS contract laboratory.

Software Development -- The most significant mainframe software development projects during FY 1986 were the completion of TDMS 2.0 Phase I and the separation of software, JCL, and data bases between NCTR and NIEHS. Development of microcomputer systems included Advanced Format, Diagnostics, DISKCOPY, CP/M Utilities, and File Handling Utilities. In addition, design work was done on the TDMS 2.0 Phase II.

All NCTR software development activities for NTP ended on September 30, 1986. During the last two quarters of FY 1986, the major part of software development resources were devoted to the transition of support activities from NCTR to the NIEHS software support contractor.

Software Maintenance and Enhancement -- Major enhancements to EIS and PEIS microcomputer systems included improvements in report requests, utility programs, touchscreen calibration, and transaction log request. Mainframe enhancements resulted in 19 different report changes. The majority of software maintenance on the mainframe was to resolve report data exceptions.

All NCTR software maintenance and enhancement activities for NTP ended on September 30, 1986. During the last two quarters for FY 1986, a major part of these resources was devoted to the transition of support activities from NCTR to the NIEHS software support contractor.

Central Computer Support -- FY 1986 saw a continued growth of 30 to 40 percent for NTP in both the number of transitions processed and the number of animal and cage records on the NCTR central computer. System and hardware monitors were installed, resulting in a fifty percent reduction in unplanned outages and in more effective load balancing. In addition, significant personnel and machine resources were devoted to the transition of software support from NCTR to NIEHS. (CONTACT PERSON: Mr. Gary Green)

FY 1987 PROGRAM PLANS

The major activities for FY 1987 will include Central Computer Support and Production Control Support.

INFORMATION GENERATION AND DISSEMINATION

The effective deployment of scientific information about the properties and biological activities of toxic or potentially toxic chemical substances is an element which is a critical component of the basic goals of the National Toxicology Program. The dissemination of such information forms the bases for identifying and/or initiating the resolution of many human health and environmental concerns relevant to chemical substances.

The NTP continues to solicit involvement from both public and private sector organizations in order to enhance quality and relevance in selection and evaluation of chemical substances. These organizations include: Federal, state and local governments; trade associations; industry; labor; academia; professional societies; public interest groups; the press; individuals; other countries; and other interested parties. Among the types of information received are: nominations of chemicals to be tested; critiques and questions about scientific procedures, policies, priorities, and resource allocations; suggestions for program improvement; and most importantly, information about planned, ongoing, and recently completed studies on chemicals being considered for toxicology evaluation or being studied by the NTP.

In FY 1986 as part of an effort to inform the public and allow interested parties to comment and provide information on chemicals prior to designing long-term toxicology and carcinogenesis studies, the NTP began to routinely announce in the Federal Register the list of chemicals for which short-term toxicology studies have been completed. Parties with relevant information will be asked to communicate in writing or by telephone with the NTP scientist responsible for the study. Information received may be used in the design of chronic and special studies.

Scientific Coordination and Information Dissemination -- The NTP Board of Scientific Counselors convenes two to three times a year in public forum, as does the Board's Peer Review Panel whose members evaluate draft technical reports on toxicology and carcinogenesis studies.

To foster early awareness of toxicologic hazards, the NTP has adopted the policy of notifying staff from participating agencies and other interested parties, including labor and affected industries, that on the basis of preliminary pathology data, certain chemicals under study by the NTP may pose potential public health problems. Notifications are sent out only on those studies in which the preliminary findings are highly significant statistically. Early notification alerts the agencies to potential problems and enables them to develop long-range contingency plans for the allocation of resources for possible exposure and regulatory analyses. Further, it enhances the dialogue between NTP staff and regulatory agency personnel and can lead to more extensive and relevant testing to characterize the toxic potential of these chemicals.

To remain aware of scientific procedures and results produced by other laboratories, the second part of the Annual Plan, the Review of Current DHHS, DOE and EPA Research Related to Toxicology, contributes toward this goal. This document provides overviews of research programs as well as information on chemicals being studied and toxicologic methods development activities in the various agencies. Work in progress and communication links among investigators worldwide are integrated with many national and international organizations and are being pursued with others.

Fundamental to current awareness is the ready availability of comprehensive searches and reviews of the scientific and technical literature on a given compound in advance of decisions about priorities for study and experimental designs. This is of special importance for the toxicology and carcinogenesis studies program, where the study process for each chemical represents a major commitment of time, labor, materials and funds for up to a five-year period. The online services from the National Library of Medicine (NLM) are particularly valuable for this purpose. These are CHEMLINE, TOXLINE, MEDLINE, CANCERLINE, HSDB (Hazardous Substances Data Bank), and RTECS (Registry of Toxic Effects of Chemical Substances). These and other sources (e.g., IARC Monographs, Surveys of Compounds Which Have Been Tested for Carcinogenic Activity, PHS, 1951-1980) are used to prepare dossiers on chemicals nominated for study and to provide information for the design of protocols. (CONTACT PERSONS: Dr. M. Spann, NLM, and Ms. S. Soward, NIEHS)

The Environmental Mutagen, Carcinogen, and Teratogen Information Program, which receives funding from the NTP, collects, organizes, and disseminates, primarily. published information on chemicals tested for mutagenicity, and maintains the EMIC computerized data file. Located since its inception in 1969 at the Oak Ridge National Laboratory (ORNL), the EMIC file contained (as of July 1986) 60,158 records on over 20,000 unique agents, 49,721 of which are available on-line from TOXLINE (at the NLM) and 58,111 from RECON (at the ORNL). Each record contains bibliographic information, assay systems, and keywords defining agents tested and organisms studied. (CONTACT PERSONS: Mr. S. Stasiewicz, NIEHS, and Mr. J. S. Wassom, ORNL)

The Environmental Teratology Information Center (ETIC) was established in 1975. Through an Interagency Agreement with the Department of Energy (DOE), the services and facilities of the ORNL were obtained to maintain this computerized information system. The ETIC file contains references to published literature (3,544 different journals, books, reports, etc.) about environmental agents tested for or known to induce teratogenic effects. As of September 30, 1986, a total of 41,499 references had been collected with 39,520 available through the National Library of Medicine TOXLINE file. These references contain information about 7,300 unique chemical agents identified with the Chemical Abstract Service (CAS) Registry numbers and 875 agents without CAS numbers. Each record is indexed with bibliographic information, language, publication type, systems studied or systems affected by test agent, keywords defining agents tested, CAS number and organisms studied. (CONTACT PERSONS: Ms. S. Soward, NIEHS, and Mr. J.S. Wassom, ORNL)

As an out reach activity, the NTP Technical Information and Scientific Evaluation Group (TISEG) manned an NTP display at the annual Teratology Society meeting (July 8-10, 1986) and the Annual Behavioral Teratology Society meeting (July 6-8, 1986). The display included a table-top exhibit denoting NTP program structure, organization and funding; copies of NTP publications; and a computer terminal for doing searches of the ETIC file or the CHEMTRACK system. The TISEG staff distributed 941 documents and performed 35 computerized searches about 68 different subjects.

Technical Report Preparation and Dissemination -- Chemical managers (toxicologists) use the relevant information to design experiments and to oversee the progress of a compound from selection through toxicology and carcinogenesis experiments to final report preparation and distribution. Preparation of the technical report begins with selection of a chemical for study and the appointment of a chemical manager. Each manager is responsible for recommending and designing the appropriate experiments, for records management and experiments monitoring throughout the study period, for preparation of the draft toxicology and carcinogenesis technical reports, and for presenting/defending these draft technical reports before the Peer Review Panel. While experiments are in progress, the chemical manager interacts with other Government agencies and industry and serves as the resource person for scientific inquiries concerning the chemical and its possible adverse effects. Lists of chemicals nominated and scheduled for toxicology study, those being studied and those completed are published in the Federal Register and the NTP Annual Plan as well as being distributed to a variety of newsletters and scientific magazines.

Data from the toxicologic characterization studies and the chronic exposure experiments are collected into comprehensive and evaluative technical reports. After the draft receives staff approval, copies are sent for external peer review to the NTP Board of Scientific Counselors' Peer Review Panel. At this stage draft reports are made available to any individual or organization seeking or requesting copies. The Peer Review Panel, comprised of non-government scientists, then reviews critically these draft reports and gives their opinions and findings in sessions open to the public. Routinely, comments and questions are requested from the individuals or groups attending these open meetings. After the draft reports are considered by staff and the Peer Review Panel to be scientifically acceptable and soundly based, the technical reports undergo a final technical and style edit prior to printing and distribution. The recommendations of the reviewers and summary comments recorded at the meeting are incorporated where appropriate and relevant in the final revision of the report. Draft summary minutes for each report review are sent to the reviewers for comments and approval. Edited minutes are made available for distribution to any interested party.

Meetings to perform peer review of NTP draft technical reports are held three times yearly, usually in Research Triangle Park, N.C. A list of the reports to be reviewed, reviewer assignments, review forms, and other information about a particular meeting are sent to Peer Review Panel members prior to the meeting date. At the same time, notices of the meeting are published in the Federal Register. (CONTACT PERSON: Dr. L. Hart, NIEHS)

Tracking of Chemical Testing Status -- An on-line computer data base system (called CHEMTRACK) has been developed for tracking chemicals in various stages of toxicology and carcinogenicity testing. A report was developed which describes the status of NTP chemicals in the various stages of each test program. This report is distributed quarterly on an individual basis to those who want to know about progression of chemicals through the Program. (CONTACT PERSONS: Ms. S. Soward, and Mr. M. Rowley, NIEHS)

International Coordination -- In partnership with the international community, the NTP strives to formulate a universally-based communication network of toxicologic information, and in particular, in the area of chemical carcinogenesis. Concomitantly, the NTP is seeking active participation from toxicologists and other agencies throughout the world. For instance, contacts are maintained with the World Health Organization (WHO), with the International Program on Chemical Safety (IPCS), with the International Agency for Research on Cancer (IARC), with the International Registry of Potentially Toxic Chemicals (IRPTC), with the United Nations Environment Program (UNEP), with the European Chemical Industry Ecology and Toxicology Center (ECETOX), and with governments and individual scientists throughout the world. As an example, an agreement still in existence was entered into with the IARC, in July 1981, to establish and maintain an international registry of persons exposed to phenoxy herbicides and contaminants, particularly the chlorinated dibenzodioxins and dibenzofurans. This registry complements the national effort under the guidance of NIOSH. (CONTACT PERSON: Dr. J. Huff, NIEHS)

AN NTP/EPA interagency effort has been continued to maintain a worldwide clearinghouse on phthalate research activities. Information is being collected, catalogued, and stored, primarily about ongoing research and testing efforts; an international registry of scientists engaged in phthalates research is being assembled, and in certain voluntary instances preliminary or recently completed research and testing results will be received and made available. (CONTACT PERSON: Mrs. S. Soward, NIEHS)

The Technical Information and Scientific Evaluation (TISEG) Group is cooperating in a pilot version of the United States National Implementation Plan (NIP) for the Office for Economic Cooperation and Development (OECD) Improved Access to Unpublished Information Project (Switchboard). In this pilot project we exchange unpublished chemical information with the United Kingdom, Germany, Japan, Sweden and the Netherlands. Within the United States the National Implementation Plan (NIP) functions as a hybrid system in which requests are routed through an "International Focal Point" and a network of National Focal Points (NFPs) which connect a requester with potential information holders. The United States NFP is the Office of Toxic Substances, Environmental Protection Agency. From October 1, 1985, through September 30, 1986, TISEG processed 34 Switchboard requests from the United Kingdom, Japan, Sweden and the Netherlands. (CONTACT PERSONS: Mrs. S. Soward, NIEHS, Mr. R. Sloane, NIEHS, and Ms. L. Travers, EPA)

Public Information Office (PIO) -- The PIO responds to inquiries from the press and others regarding NTP programs and studies results and distributes NTP publications. In addition, the staff of the PIO maintains the mailing list for the following:

- NTP Annual Plan (including Review of Current DHHS, DOE, and EPA Research Related to Toxicology);
- Technical Reports on NTP toxicology and carcinogenesis studies;
- Annual Report on Carcinogens, prepared for the Secretary of DHHS;

- Summary minutes of NTP Board of Scientific Counselors and Peer Review Panel meetings.

Questions about the NTP and requests for publications or inclusion on the mailing list should be directed to: NTP Public Information Office, MD B2-04, Box 12233, Research Triangle Park, NC 27709. Telephone: (919) 541-3991. FTS: 629-3991. (CONTACT PERSON: Ms. H. Stopinski)

ANNUAL REPORT ON CARCINOGENS

The Fourth Annual Report on Carcinogens (4th ARC) and its Summary have been prepared and are available for distribution. The ARC is prepared by NTP and NIEHS staff working with representatives from the following regulatory and research agencies: The Centers for Disease Control/National Institute for Occupational Safety and Health; the Consumer Product Safety Commission; the Environmental Protection Agency; the Food and Drug Administration; the National Institutes of Health: National Cancer Institute/National Institute of Environmental Health Sciences/National Library of Medicine; and the Department of Labor/Occupational Safety and Health Administration.

The ARC is prepared in response to a 1978 amendment [Section 301 (b) (4)] to the Public Health Service Act which requires the Secretary of the Department of Health and Human Services (DHHS) to publish annually a list of "all substances which are either known to be carcinogens or which may reasonably be anticipated to be carcinogens and to which a significant number of persons residing in the United States are exposed..." The Secretary, DHHS, has delegated the preparation of this report to the Director, NTP.

The 4th ARC includes 117 entries from the 3rd ARC as well as 31 additional entries. These entries (new and old) have been selected from among those chemicals, mixtures or occupational exposures: (1) for which the International Agency for Research on Cancer (IARC) has determined there is sufficient or limited evidence of carcinogenicity in humans, or sufficient evidence of carcinogenicity in experimental animals; (2) that are regulated by the Federal Government as carcinogens; (3) that have been found to cause cancer in long-term studies in animals as conducted by the National Cancer Institute or the NTP; or (4) that have been suggested for inclusion by the agencies involved in preparing the ARC.

Each entry in the 4th ARC includes: summaries of the human or animal evidence for carcinogenicity; data on production, occurrence and use of this chemical/substance when appropriate/available; a list of regulations about this entry; and information on the route and amounts of human exposure. The ARC appendices contain lists of some synonyms for the entries, a CAS number list of all entries, a glossary of terms and acronyms, and a list of requests to the Department of Health and Human Services (DHHS) for information about carcinogens listed in the ARC.

The 4th ARC underwent a series of peer reviews by NTP staff as well as representatives of Federal regulatory and research agencies and programs within and outside the DHHS. Public review of the draft 4th ARC was elicited by a notice in the Federal Register (in December 1985). These comments were considered and peer reviewed in the same way as were the original entries, and a number of changes were made in the draft 4th ARC before its final approval by the Secretary, DHHS, in July 1986.

The 5th (next) ARC is now in various parts of the review and editing stages. Public comments on the proposed new entries/additions and editorial changes in this 5th ARC was solicited by a notice in the Federal Register (published in October 1986). These comments will be peer reviewed by the various committees as was done for the 4th ARC, and a draft of the 5th ARC submitted to the Secretary, DHHS, for approval as soon as possible (perhaps by early 1987). (CONTACT PERSON: Dr. J.R. Fouts, NIEHS)

Copies of the Summary of the 4th ARC have been sent to the mailing list and can be obtained by request to NTP Public Information Office, MD B2-04, P.O. Box 12233, Research Triangle Park, N.C. 27709, Tel. No. (919) 541-3991; FTS 629-3991.

Copies of the complete 4th ARC are available for a fee from the National Technical Information Service (NTIS), U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161; Tel. No. (703) 487-4650.

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APPENDICES

APPENDIX A

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NCTR

Dr. Ronald W. Hart, Director

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Dr. Ernest E. McConnell, Director, Division of Toxicology Research and Testing

NIOSH

Dr. Janet C. Haartz, Director, Division of Biomedical and Behavioral Science

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The following alphabetical list includes NTP agency program leaders, project officers, and other key agency staff who should be contacted for further information about activities described in this NTP Annual Plan for FY 1987.

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APPENDIX A (Continued)

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APPENDIX A (Continued)

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APPENDIX A (Continued

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---

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NIOSH/OH = National Institute for Occupational Safety and Health, 4676 Columbia Parkway, Cincinnati, Ohio 45226

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NLM = National Library of Medicine, Bethesda, Maryland 20014

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**Telephone Numbers:

The first number given after a person's name is the commercial number; the second is the FTS number. When only one number is listed, this can be used as commercial or FTS. The area codes for commercial numbers are as follows: EPA - (202); FDA - (301); NCTR - (501); NIEHS/MD - (301); NIEHS/NC - (919); NIOSH/OH - (513); NIOSH/WV - (304); NLM - (301); ORNL/TN - (615).

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